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(21) International Application Number: PCT/US97/05744 (22) International Filing Date: 7 April 1997 (07.04.97) (30) Priority Data: 60/016,295 12 April 1996 (12.04.96) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventor: ROBL, Jeffrey, A.; 7 Tulip Drive, Newtown, PA 18940 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: N-FORMYL HYDROXYLAMINE CONTAINING COMPOUNDS USEFUL AS ACE INHIBITORS AND/OR NEP INHIBITORS (57) Abstract <p>N-formyl hydroxylamines are provided which have structure (I) wherein R and R¹ are as defined herein and A is a dipeptide derived from an amino acid or is a conformationally restricted dipeptide mimic.</p> <div data-bbox="1071 1165 1364 1291"></div>		

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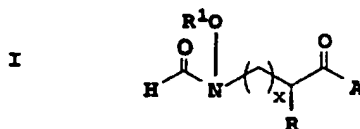
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N-FORMYL HYDROXYLAMINE CONTAINING COMPOUNDS
USEFUL AS ACE INHIBITORS AND/OR NEP INHIBITORS

Summary of the Invention

5 This invention is directed to novel compounds possessing angiotensin converting enzyme (ACE) inhibitory activity and/or neutral endopeptidase (NEP) inhibitory activity and methods of preparing such compounds. This invention is
10 also directed to pharmaceutical compositions containing such ACE and/or NEP inhibiting compounds or pharmaceutically acceptable salts thereof and the method of using such compositions.

15 The compounds of this invention are those of the formula (I)



including a pharmaceutically acceptable salt thereof where:

20 x is 0 or 1;

 R is H, alkyl, alkenyl, aryl-(CH₂)_p-, heteroaryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, or

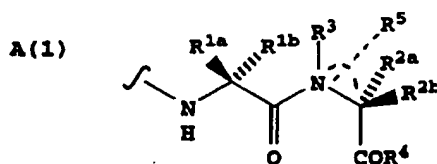
 R can be joined together with the carbon to which it is attached to form a 3 to 7 membered ring
25 which may optionally be fused to a benzene ring;

 R¹ is H or -COR² where R² is alkyl, aryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, heteroaryl-(CH₂)_p-, alkoxy, or cycloalkyl-(CH₂)_p-;

 p is 0 or an integer from 1 to 8; and

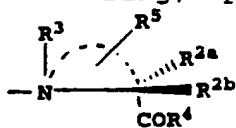
30 A is a dipeptide derived from one or two non-proteinogenic amino acid or is a conformationally restricted dipeptide mimic as described below.

 A is a dipeptide derivative of the
35 structure



where R^{1a} , R^{1b} , R^{2a} and R^{2b} are independently selected from H, alkyl, aryl-(CH₂)_p-, cycloalkyl, cycloheteroalkyl-(CH₂)_p-, heteroaryl-(CH₂)_p-, biphenylmethyl, or

R^{1a} and R^{1b} or R^{2a} and R^{2b} may be joined together to the carbon to which they are attached to form a 3 to 7 membered ring, optionally fused to



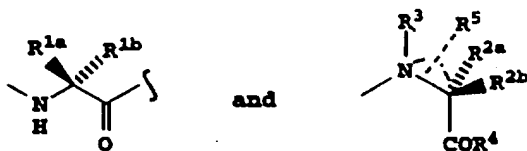
a benzene ring; and refers to an optional 5 or 6 membered ring containing a single hetero atom and which may optionally include an R^5 substituent (as shown) which is H, alkyl, aryl-(CH₂)_p or cycloalkyl-(CH₂)_p, cycloheteroalkyl-(CH₂)_p, or cycloheteroaryl-(CH₂)_p-;

R^3 is H, alkyl or aryl -(CH₂)_p-;

R^4 is OH, Oalkyl, O-(CH₂)_paryl- or NR₁(R₂)

where R_1 and R_2 are independently H, alkyl, or aryl(CH₂)_p or heteroaryl-(CH₂)_p-;

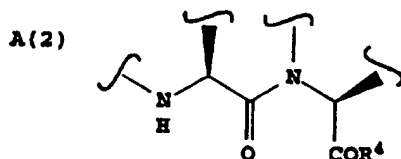
with the proviso that in A(1) at least one of



is other than a natural α -amino acid, and thus must be other than valine, leucine, phenylalanine, tyrosine, serine, cysteine, threonine, methionine, aspartic acid, glutamic acid, arginine, lysine or proline.

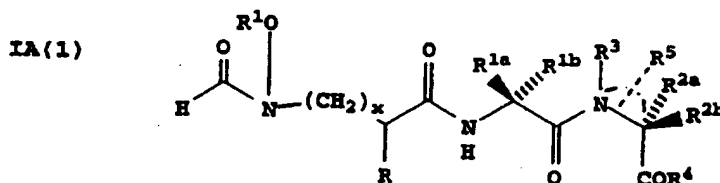
In addition, A can be a conformationally restricted dipeptide mimic which has the structure

30



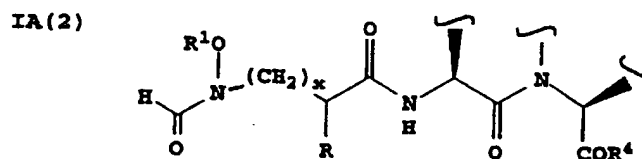
and is a non-proteinogenic dipeptide.

Thus, the compound of formula I include



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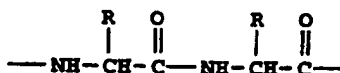
and



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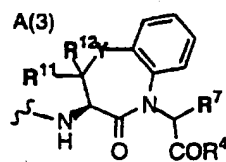
The term "conformationally restricted dipeptide mimic" refers to a structural skeleton which has the attributes of a conventional dipeptide

15

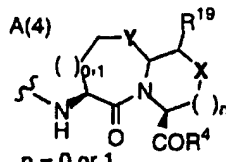


but having enhanced biological properties due to additional bonds which limit the rotational freedom.

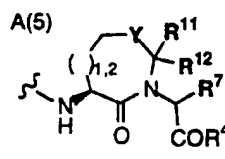
20 Examples of the A(2) dipeptide mimics include any of the conformationally restricted dipeptide mimics set out below.



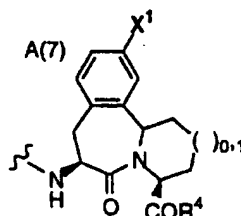
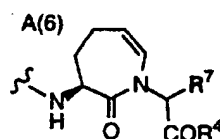
where Y = O, S, CH₂
or S(O)_{0,1,2}



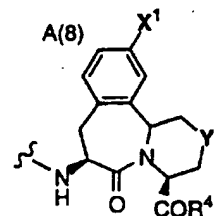
n = 0 or 1
where X = CH₂ and
Y = O, S, CH₂ or S(O)_{0,1,2}
and X = O, S when n = 1



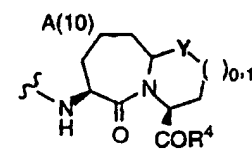
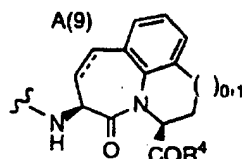
where Y = O, S, CH₂
or S(O)_{0,1,2}



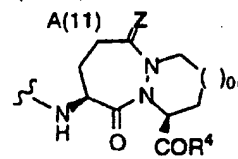
where X¹ = H, Ph,
NHSO₂R⁵
(R⁵ H)



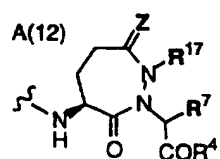
where Y¹ = O, S, NH
or S(O)_n,
where X¹ = H, Ph,
NHSO₂R⁵
(R⁵ H)



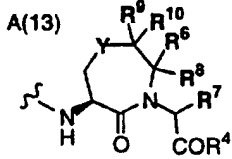
where Y = O, S, CH₂
or S(O)_{0,1,2}



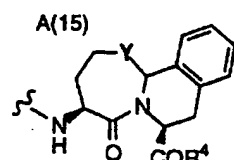
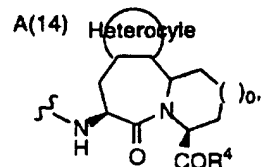
where Z = O or H, H



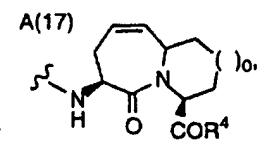
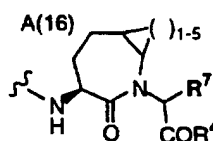
where Z = O or H, H



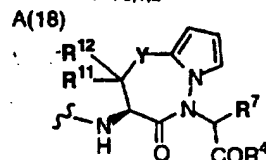
where Y = O, S, CH₂
or S(O)_{0,1,2}



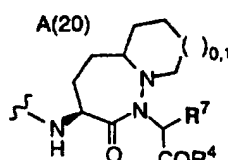
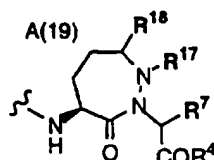
where Y = O, S,
or S(O)_{0,1,2}

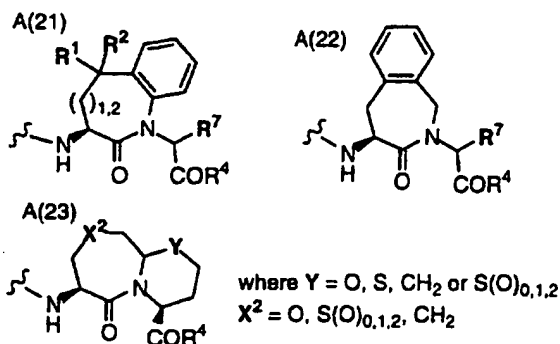


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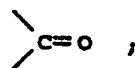


where Y = O, S, CH₂





With respect to A(5), R¹¹ and R¹² are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl -(CH₂)_m-, aryl -(CH₂)_m-, substituted aryl -(CH₂)_m-, and heteroaryl -(CH₂)_m-, or R¹¹ and R¹² taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, or R¹¹ and R¹² taken together with the carbon to which they are attached complete a keto substituent, i.e.,

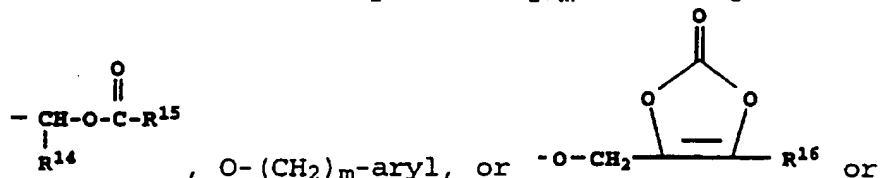


with respect to A(13) R⁸, R⁹ and R⁷ are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl -(CH₂)_m-, aryl-(CH₂)_m-, substituted aryl-(CH₂)_m-, and heteroaryl-(CH₂)_m-;

R¹⁰ and R⁶ are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl -(CH₂)_m-, aryl-(CH₂)_m-, substituted aryl -(CH₂)_m-, and heteroaryl-(CH₂)_m-, or R⁶ and R¹⁰ taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, R⁶ and R⁸ taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, or R⁹ and R¹⁰ taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons;

m is zero or an integer from 1 to 6;

R⁴ is OH, Oalkyl, O-(CH₂)_m-heteroaryl,



NR₁(R₂);

5 where R₁ and R₂ are independently H, alkyl, aryl(CH₂)_p, aryl or heteroaryl;

R¹⁴ is hydrogen, lower alkyl, cycloalkyl, or phenyl;

R¹⁵ is hydrogen, lower alkyl, lower alkoxy or phenyl;

R¹⁶ is alkyl or aryl-(CH₂)_m-; and

R¹⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl-(CH₂)_m-, aryl-(CH₂)_m-, substituted aryl-(CH₂)_m-, or

15 heteroaryl-(CH₂)_m-.

R¹⁸ is H, alkyl or alkenyl, and R¹⁸ and R¹⁷ may be taken together with the carbon and nitrogen to which they are attached to complete a saturated N-containing ring of 5 or 6 ring members.

20 R¹⁹ is H or an alkyl, and in A(4), R¹⁹ and X (which is CH₂) together with the carbons to which they are attached may form an aromatic ring of carbons (as in A(15)).

The starting compounds H-A(1) and H-A(2) are described in the literature or are obtained by modifications of known procedures. For example, the starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(5), A(13), A(16), A(21), where Y (where present) is CH₂ are disclosed by Thorsett et al., J. Med. Chem., 29, p. 251 - 260 (1988), Harris et al. in U.S. Patents 4,587,050, 4,587,238, 4,629,787 and Yanagisawa et al. in U.S. Patent 4,734,410.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(3) and A(13) where Y is S(O)_n are disclosed by Yanagisawa et al., J., Med. Chem., 30,
5 p. 1984 - 1991 (1987) and 31, p. 422 - 428 (1988), Karanewsky in U.S. Patent 4,460,579, Cheung et al. in U.S. Patent 4,594,341, and Yanagisawa et al. in U.S. Patent 4,699,905.

The starting compounds of formula H-A(1) or
10 H-A(2) wherein A(1) or A(2) is as defined in formula A(5) are disclosed by Karanewsky in U.S. Patents 4,460,579 and 4,711,884.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
15 formulas A(3) (Y is -CH₂-, and A(21) are disclosed by Watthey et al., J. Med. Chem., 28, p. 1511 - 1516 (1985) and Watthey in U.S. Patents 4,410,520, 4,470,988, 4,473,575, 4,537,885 and 4,575,503 and also by Parsons et al., Biochemical & Biophysical
20 Research Comm., 117, p. 108 - 113 (1983) and in U.S. Patent 4,873,235.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
formula A(3) and Y is S or O are disclosed by Slade
25 et al., J. Med. Chem., 28, p. 1517 - 1521 (1985) and in U.S. Patent 4,477,464 and Itoh et al., Chem. Pharm. Bull., 34, p. 1128 - 1147 (1986) and 34, p. 2078 - 2089 (1986) as well as Sugihara et al. in U.S. Patent 4,548,932 (Y is O) and Katakami et al.
30 in U.S. Patent 4,539,150 (Y is S).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
formula A(16) can be prepared by reduction of the
corresponding starting compounds wherein A(1) or
35 A(2) is as defined in formula A(3).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in

formula A(22) are disclosed by Flynn et al in U.S. Patent 4,973,585.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
5 formula A(10) and Y is S, -SO, or -SO₂ are disclosed by Harris et al. and Patchett et al. in U.S. Patents 4,415,496 and 4,617,301.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
10 formula A(10) and Y is CH₂, and is as defined in formula A(23) where X² is CH₂ is disclosed by Thorsett, Actual. Chim. Ther., 13, p. 257-268 (1986).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
15 formulas A(11) and A(19) and A(20) are disclosed by Attwood et al., Federation of European Biochemical Studies, 165, p. 201-206 (1984) and in U.S. Patent 4,512,994 and Natoff et al., Drugs Of The Future,
20 12, p. 475-483 (1987).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(12) are disclosed by Huang et al. in U.S. Patent 4,465,679.

25 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(18) are disclosed by Bolos et al. in Tetrahedron, 48, p. 9567-9576 (1992).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
30 formulas A(4) and A(15) are disclosed in European Patent Application 0629627A2.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in
35 formula A(9) are disclosed in U.S. application Serial No. 100,408 (file HA611a).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(7) and A(8) are disclosed in European Patent Application 481,522 (Flynn et al) and
5 European Patent Application 0534363A2 (Warshawsky et al).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(14) are disclosed in U.S. application
10 Serial No. 153,854 (file HA615).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(17) are disclosed in European Patent Application 0599444A1 (Barrish et al).

15 In addition, in accordance with the present invention, a pharmaceutical composition is provided which includes a therapeutically effective amount of compound I and a pharmaceutically acceptable carrier therefor.

20 The pharmaceutical composition as defined above will be useful in the treatment of cardiovascular diseases such as hypertension and/or congestive heart failure.

Furthermore, in accordance with the present
25 invention, a method is provided for treating a cardiovascular disease such as hypertension and/or congestive heart failure, as well as other diseases as set out hereinafter, which includes the step of administering to a mammalian species, including
30 humans, dogs and cats, a therapeutically effective amount of a composition as defined above.

Detailed Description Of The Invention

The term "alkyl" or "lower alkyl" refers to
35 straight or branched chain radicals having up to and including ten carbon atoms, preferably up to and including six carbon atoms, which may

optionally include one, two, or three substituents including a hydroxy, amino, alkyl, cycloalkyl, aryl, halo, trifluoromethyl, cyano, -NH(lower alkyl), -N(lower alkyl)₂, lower alkoxy, lower alkylthio, carboxy or heteroaryl.

The term "alkenyl" refers to straight or branched chain radicals of 3 to 10 carbon atoms having one or two double bonds, preferably straight chain radicals of 3 to 5 carbons having one double bond, which may optionally be substituted with one, two or three substituents including alkyl, aryl, cycloalkyl, hydroxy, amino, halo, trifluoromethyl, cyano, -NH(lower alkyl), -N(lower alkyl)₂, lower alkoxy, lower alkylthio, carboxy or heteroaryl.

The terms "alkoxy" or "lower alkoxy" and "alkylthio" or "lower alkylthio" refer to such alkyl groups as defined above attached to an oxygen or sulfur.

The term "cycloalkyl" refers to saturated rings of 3 to 7 carbon atoms.

The term "halo" refers to chloro, bromo, fluoro, and iodo.

The term "aryl" refers to aromatic groups containing 6 to 10 carbons, preferably phenyl, 1-naphthyl, and 2-naphthyl, which may optionally contain one, two or three substituents selected from alkyl, alkoxy, alkylthio, halo, hydroxy, trifluoromethyl, -SO₂NH₂, amino, -NH(lower alkyl), or -N(lower alkyl)₂, di- and tri-substituted phenyl, 1-naphthyl, or 2-naphthyl, wherein said substituents are preferably selected from methyl, methoxy, methylthio, halo, hydroxy, and amino.

The term "heteroaryl" refers to unsaturated rings of 5 or 6 atoms containing one or two O and S atoms and/or one to four N atoms provided that the total number of hetero atoms in the ring is 4 or less, which may optionally be substituted with one,

two or three substituents which include alkyl, aryl, cycloalkyl, alkoxy or halo. The heteroaryl ring is attached by way of an available carbon or nitrogen atom. Preferred heteroaryl groups include

5 2-, 3-, or 4-pyridyl, 4-imidazolyl, 4-thiazolyl, 2- and 3-thienyl, and 2- and 3-furyl. The term heteroaryl also includes bicyclic rings wherein the five or six membered ring containing O, S, and N atoms as defined above is fused to a benzene or

10 pyridyl ring. Preferred bicyclic rings are 2- and 3-indolyl and 4- and 5-quinolinyl. The mono or bicyclic heteroaryl ring can also be additionally substituted at an available carbon atom by a lower alkyl, halo, hydroxy, benzyl, or cyclohexylmethyl.

15 Also, if the mono or bicyclic ring has an available N-atom such N atom can also be substituted by an N-protecting group such as



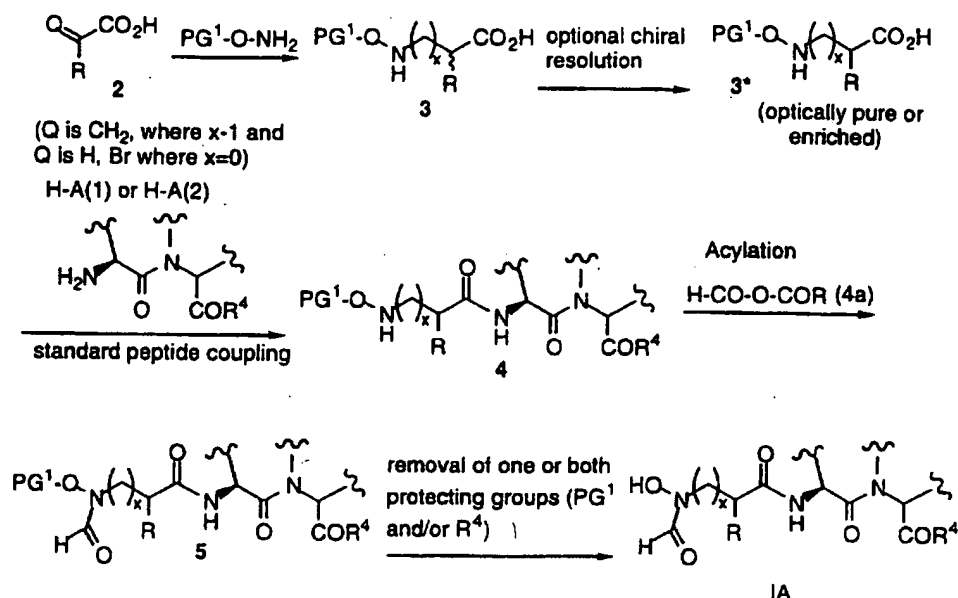
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2,4-dinitrophenyl, lower alkyl, benzyl, or benzhydryl.

The compounds of formula I of the invention may be prepared as outlined in Reaction Scheme I

25 set out below (where x is 0 or 1).

Reaction Scheme I



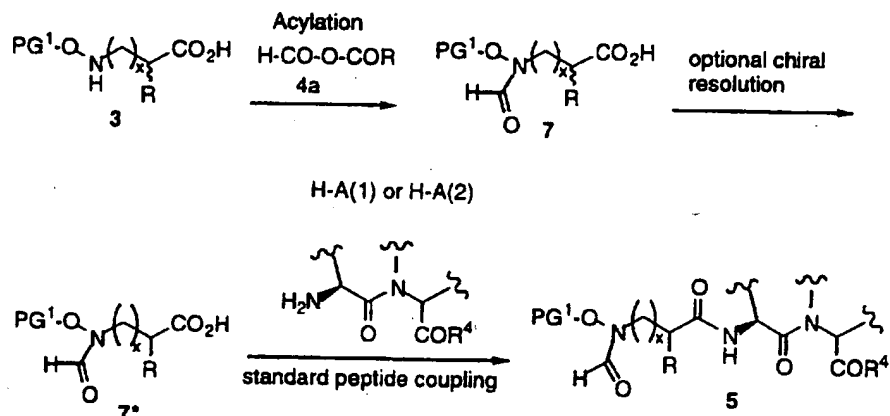
5 As shown in Scheme I, acid 2 may be reacted with a suitably O-protected (e.g. PG¹ is benzyl, p-methoxybenzyl, tetrahydropyranyl, trityl, benzhydryl, etc.) hydroxylamine to give the adduct 3. Compound 3 may be coupled directly with amine
10 H-A(1) or H-A(2) to give a mixture of diastereomers which may be separated or preferably compound 3 may be optically enriched or purified, employing conventional techniques, to give 3*. Subsequent coupling with H-A(1) or H-A(2) gives 4
15 in diastereomerically enriched or pure form. Reaction of the hydroxylamine nitrogen of 4 with a formylating agent affords 5. At this point one or both protecting groups may be removed, either sequentially or simultaneously, to produce compound
20 of the invention IA. For example, when PG¹ is benzyl and R⁴ is Obenzyl, both may be removed by hydrogenolysis. When PG¹ is benzyl and R⁴ is -Omethyl or -Oethyl, the PG¹ group may be removed by hydrogenolysis and the ester group may be
25 converted to the acid by base hydrolysis. PG¹

groups such as THP or trityl may be removed by treatment with strong acid such as hydrogen chloride or trifluoro acetic acid in a protic solvent.

- 5 Alternately, compounds of the invention IA may be obtained by the route depicted in Scheme II (where x is 0 or 1).

Reaction Scheme II

10



- As seen in Reaction Scheme II, compound 3 may be formylated with an formylating agent 4a to give acid compound 7. This acid may be coupled with A(1) or A(2) directly or optically resolved to give 7* and then coupled to give compound 5. Compound 5 is then converted to compound of the invention IA as described above.

- 20 The compounds of formula I of the invention contain one or more asymmetric centers. Thus, these compounds can exist in diastereoisomeric forms or in mixtures thereof and all of such forms are within the scope of this invention. The above
25 described processes can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric compounds are prepared, they can be separated by conventional

chromatographic or fractional crystallization methods.

The compounds of formula I of the invention can be isolated in the form of a pharmaceutically acceptable salt. Suitable salts for this purpose are alkali metal salts such as sodium and potassium, alkaline earth metal salts such as calcium and magnesium, and salts derived from amino acids such as arginine, lysine, etc. These salts are obtained by reacting the acid form of the compound with an equivalent of base supplying the desired ion in a medium in which the salt precipitates or in aqueous medium and then lyophilizing.

The compounds of formula I of the invention are inhibitors of angiotensin converting enzyme and/or neutral endopeptidase. Thus, the compounds of formula I including their pharmaceutically acceptable salts are useful in the treatment of physiological conditions in which either angiotensin converting enzyme inhibitors or neutral endopeptidase inhibitors have been shown to be useful. Such conditions include cardiovascular diseases, particularly, hypertension, congestive heart failure, renal failure, and hepatic cirrhosis, as well as analgesic activity. The compounds of formula I are also inhibitors of other metalloproteases such as the matrix metalloproteases, for example, gelatinase, collagenase and stromelysin and thus are useful in the treatment of osteoarthritis, rheumatoid arthritis, metastatic tumors, and angiogenesis.

Diuresis, natriuresis, and blood pressure reduction are produced in a mammalian host such as man by the administration of from about 1 mg. to about 100 mg. per kg. of body weight per day, preferably from about 1 mg. to about 50 mg. per kg.

of body weight per day, of one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof. The compounds of formula I are preferably administered orally, but
5 parenteral routes such as subcutaneous, intramuscular, and intravenous can also be employed. The daily dose can be administered singly or can be divided into two to four doses administered throughout the day.

10 The ACE and/or NEP inhibitors of formula I can be administered in combination with human ANF 99 - 126. Such combination would contain the inhibitor of formula I at from about 1 to about 100 mg. per kg. of body weight and the human ANF 99 -
15 126 at from about 0.001 to about 0.1 mg. per kg. of body weight.

The ACE and/or NEP inhibitors of formula I can be administered in combination with other classes of pharmaceutically active compounds. For
20 example, a calcium channel blocker, a potassium channel activator, a cholesterol reducing agent, etc.

The ACE and/or NEP inhibitors of formula I or a pharmaceutically acceptable salt thereof and
25 other pharmaceutically acceptable ingredients can be formulated for the above described pharmaceutical uses. Suitable compositions for oral administration include tablets, capsules, and elixirs, and suitable compositions for parenteral
30 administration include sterile solutions and suspensions. About 10 to 500 mg. of active ingredient is compounded with physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavoring, etc., in a
35 unit dose form as called for by accepted pharmaceutical practice.

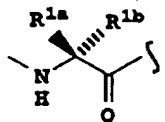
Preferred compounds of the invention are those of formula I wherein

R^1 is H,

x is 1,

5 R is alkyl or arylalkyl, and

A is A(1), preferably



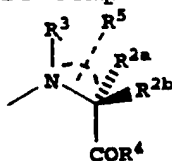
where is preferably a non-proteinogenic amino acid portion wherein,

10 R^{1a} and R^{1b} are each independently alkyl such as methyl or ethyl, or arylalkyl such as benzyl, or

R^{1a} and R^{1b} together with the carbon to which they are attached form a 3-7 membered ring, preferably a 5-membered ring, or

15 R^{1a} and/or R^{1b} is biphenylmethylene and the other may be H.

Also preferred are compounds where A is

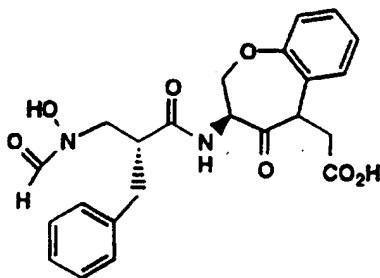


20 A(1), preferably where COR^4 and is a non-proteinogenic amino acid where R^3 is H, alkyl, such as methyl or ethyl, aryl such as phenyl, or arylalkyl, such as benzyl,

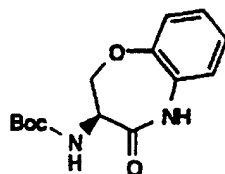
25 R^{2a} and R^{2b} are independently selected from H, alkyl, aryl, arylalkyl (with at least one of R^{2a} and R^{2b} being other than H) or R^{2a} and R^{2b} together with the carbon to which they are attached form a 3-7 membered ring, preferably 5- or 6-membered ring.

Also preferred are compounds where A is A(2) wherein R^4 is OH.

30 The following Examples represent preferred embodiments of the present invention.

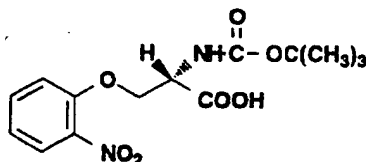
Example 1

A.



5

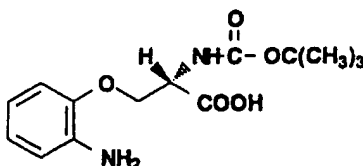
A(1).



- 10 A solution of BOC-L-serine (24.3 g, 0.118 mole) in dry dimethylformamide (25 ml) was added dropwise over a period of 1.0 hour to a cooled (0°, ice-salt bath) suspension of 60% NaH (10.1 g, 0.25 mole) in dry dimethylformamide (200 ml) and
- 15 stirring was continued at 0° until the frothing subsided (ca. 2.0 hours). The reaction mixture was treated dropwise with 1-fluoro-2-nitrobenzene (14.3 ml, 0.13 mole) over a period of 20 minutes, stirred at 0° under argon for 4.0 hours then poured into
- 20 ice-water (750 ml) and extracted with Et₂O (2 x 100 ml). The aqueous phase was brought to pH 1.0 with 6 N HCl (70 ml), extracted with EtOAc (3 x 500 ml) and the combined organic extracts were washed with brine (100 ml), dried (anhydrous Na₂SO₄),
- 25 filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck), eluting the column with

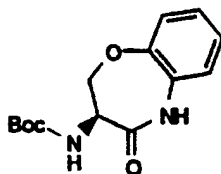
CH₂Cl₂:CH₃OH:HOAc (100:5:0.2) to give title compound as a thick yellow syrup (27.222 g, 70.7%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.27 (Silica gel; CH₂Cl₂:CH₃OH:HOAc-
5 100:5:0.5; UV, PMA).

A(2).



10 A solution of Part A(1) compound (27.1 g, 83 mmoles) in dry methanol (500 ml) was treated with 10% Pd/C (900 mg) and hydrogenated at 40 psi for 2.0 hours. The reaction mixture was filtered through a Celite® pad in a millipore unit, washing
15 the pad well with CH₃OH (5 x 100 ml). The dark filtrate was evaporated to dryness and dried in vacuo to give a dark solid. The crude product was triturated with CH₂Cl₂:Hexane (1:4) to give title compound as a light tan solid (17.69 g, 71. %) with
20 consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.15 (Silica gel; CH₂Cl₂:CH₃OH:HOAc- 20:1:1; UV).

A(3).

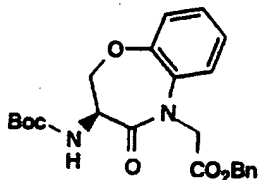


25

A solution of Part A(2) compound (16.69 g, 56.3 mmoles) in dry dimethylformamide (121 ml) was treated with 1-ethyl-3-(3-dimethylaminopropyl)-
30 carbodiimide (10.64 g, 55.5 mmoles) and stirred at room temperature for 3.0 hours. The reaction mixture was partitioned between EtOAc (2 x 492 ml)

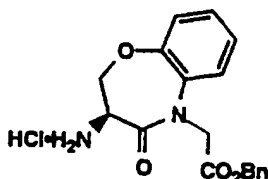
and 1.0 N NaHCO₃ (492 ml), and the combined organic extracts were washed with H₂O (3 x 492 ml), brine (492 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried in vacuo. The crude product was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane mixtures (1:4; 1:2; 1:1) to give title compound as off-white crystals (10.5 g, 72.4%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.40 (Silica gel; EtOAc:Hexane- 1:4; UV).

B.



A solution of Part A compound (640 mg, 2.30 mmol) in dry THF (12 mL) at 0°C was treated with LiN(TMS)₂ (1.0 M in THF, 2.60 mL, 2.60 mmol) followed approximately 30 seconds later with benzyl bromoacetate (475 µL, 687 mg, 3.0 mmol). After 25 minutes, the mixture was quenched with saturated NH₄Cl, diluted with H₂O, and extracted with EtOAc. The EtOAc extract was washed with H₂O and brine, then dried (Na₂SO₄), filtered and stripped to give a yellow oil. Flash chromatography (Merck SiO₂, 3/7-EtOAc/hexanes as eluant) provided title compound (967 mg, 98%) as a colorless oil/foam.

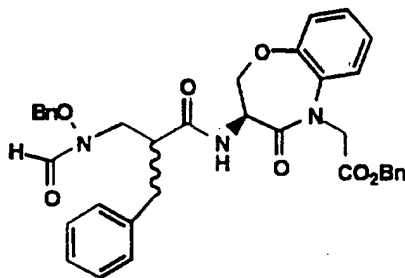
C.



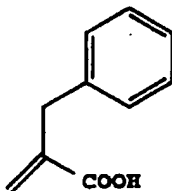
A solution of Part B compound (960 mg, 2.25 mmol) in 1,4-dioxane (4 mL) was treated with a solution of 4.0 M HCl in 1,4-dioxane (6 mL) at room temperature. After 3 hours, the mixture was concentrated in vacuo, triturated with Et₂O to give a solid and stripped to afford title compound (858 mg, 105% of theory).
m.p. 152-155°C.

10

D.



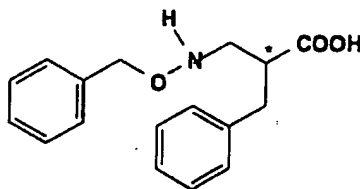
D(1).



15

A solution of benzylmalonic acid (23.06 g, 0.12 mole) in H₂O (200 mL) was treated with 37% CH₂O solution (278.4 mL) and 40% aqueous (CH₃)₂NH (35 mL, 0.31 mole) then stirred overnight at room temperature under argon. The clear solution was heated to an internal temperature of 90°C for 2.0 hours (at which time gas evolution had ceased), cooled and acidified to pH 1.0 with 12 N HCl (20 mL). The white precipitates were filtered off, washed with H₂O (3 x 25 mL) and dried in vacuo to give title compound as a white solid (12.85 g, 66.6%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.63 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV). m.p. 66-68°C.

D(2).



(J. Med. Chem. 28, 1985, 1167)

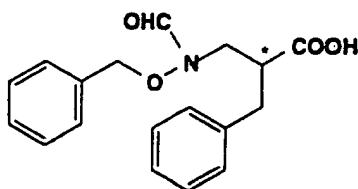
5

A solution of Part D(1) compound (8.9 g, 54.9 mmol) and O-benzylhydroxylamine (26.7 g, 0.23 mole) in absolute EtOH (9.0 ml) was refluxed for 7 days, cooled to room temperature and evaporated to dryness. The residual syrup was dissolved in 1.0 N NaOH (55 ml), stirred for 15 minutes then extracted with EtOAc (4 x 18 ml). The organic phase was washed with H₂O (3 x 10 ml) and the aqueous extracts were combined and acidified to pH 2.0 with 1.0 N HCl (62 ml). The acidic aqueous phase was then extracted with EtOAc (5 x 75 ml) and the combined organic extracts washed with H₂O (2 x 30 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product (3.93 g, 25.1%) was triturated with Et₂O:Hexane (1:4; 2 x 25 ml) and all solids obtained were dissolved in CH₂Cl₂ and filtered, washing the insoluble precipitates with CH₂Cl₂. The clear filtrate was evaporated and dried in vacuo to give title compound as an opaque colorless solid with consistent ¹H-NMR and ¹³C-NMR spectral data.

TLC: R_f 0.33 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV, PMA).

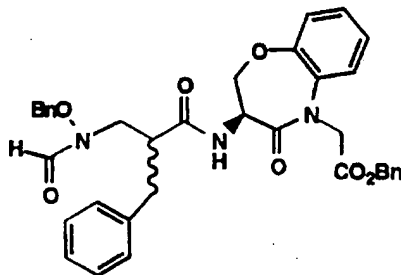
M.p. 69-71°C.

D(3).



- 5 A cooled (0°C, ice-salt bath) mixture of HCOOH (17.5ml) and acetic anhydride (Ac₂O) (1.75 ml) was stirred for 20 minutes, treated with Part D(2) compound (1.0 g, 3.5 mmoles) and stirring was continued at 0°C for another 3.0 hours. The reaction mixture was stripped to dryness,
- 10 evaporated from Et₂O (2 x 25 ml), toluene (20 ml) and hexane (2 x 50 ml) then dried in vacuo to give title compound as a thick syrup (1.096 g, 100% crude yield) with consistent
- ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.23
- 15 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV, PMA).

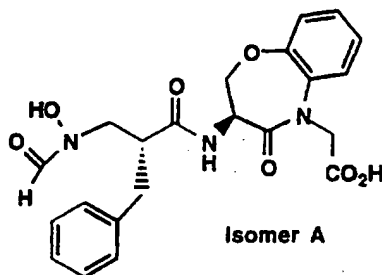
D(4).



- 20 A solution of Part D(3) compound (366 mg, 1.19 mmol) in CH₂Cl₂ (9 mL) at 0°C was treated with HOBT hydrate (210 mg) followed by EDAC (230 mg, 1.20 mmol). After 20 minutes, the mixture was treated with Part C amine hydrochloride 3 (390 mg,
- 25 1.07 mmol) followed by 4-methylmorpholine (200 µL, 184 mg, 1.8 mmol). The mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours. The reaction was partitioned between EtOAc and 5% KHSO₄. The EtOAc extract was washed successively

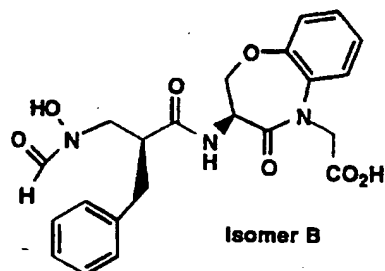
with H₂O, 50% saturated NaHCO₃ and brine, then dried (Na₂SO₄), filtered and stripped. Flash chromatography (Merck SiO₂, 50% to 60% EtOAc in hexanes as eluant) provided title compound (550 mg, 84%) as a white foam which was shown by NMR and HPLC to be a 1:1 mixture of diastereomers.

E.



10

A solution of Part D compound (535 mg, 0.87 mmol) in MeOH (10 mL) was hydrogenated (balloon) over 10% Pd/C (123 mg) at room temperature for 2.75 hours. The solvent was filtered through Celite and the filtrate was stripped to give a diastereomeric mixture of title Isomer A and Isomer B



Trituration of a solution of the residue in MeOH with Et₂O provided 350 mg of the diastereomeric mixture. Approximately 255 mg of this mixture was separated by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate 25 mL/min detecting at 220 nm; 40 to 100% B over a 30 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.1% TFA; solvent B: 10% H₂O-90% MeOH-0.1% TFA); title Isomer A t_R = 14.4 min; separation performed in three runs). The desired fractions were stripped,

azetroped with EtOAc, re-dissolved in EtOAc and triturated with Et₂O to give title Isomer A (105.5 mg) as an off-white solid.

5 MS: (M+NH₄)⁺ 459; (M-H)⁻ 440

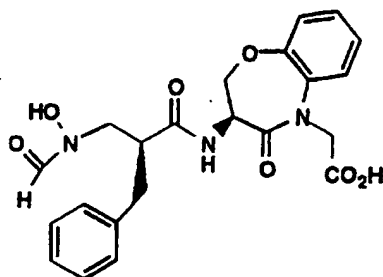
HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R=9.67 min (96.0%).

Anal. Calc'd for C₂₂H₂₃N₃O₇•1.6H₂O•0.1EtOAc•0.1Et₂O

C, 56.29; H, 5.80; N, 8.64

15 Found: C, 56.21; H, 5.15; N, 8.29.

Example 2



5 A solution of Example 1 Part E Isomers A and B (1:1 mixture of diastereomers, 535 mg, 0.87 mmol) in MeOH (10 mL) was hydrogenated (balloon) over 10% Pd/C (123 mg) at room temperature for 2.75 hours. The solvent was filtered through Celite and
10 the filtrate was stripped to give a diastereomeric mixture of Isomers A and B. Trituration of a solution of the residue in MeOH with Et₂O provided 350 mg of the diastereomeric mixture.

Approximately 255 mg of this mixture was separated
15 by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate 25 mL/min detecting at 220 nm; 40 to 100% B over a 30 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.1% TFA ; solvent B: 10% H₂O-90% MeOH-0.1% TFA); Isomer B t_R = 18.6 min; separation
20 performed in three runs). The desired fractions were stripped, azeotroped with EtOAc, re-dissolved in EtOAc and triturated with Et₂O to give Isomer B (88.0 mg) as an off-white solid.

25 MS: $(M+NH_4)^+ 459$; $(M-H)^- 440$

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 13.8 min (94.0%).

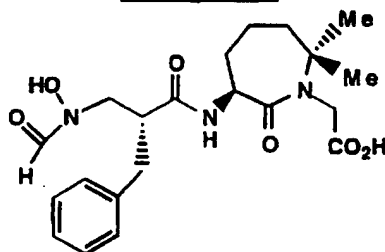
Anal. Calc'd for $C_{22}H_{23}N_3O_7 \cdot 1.5H_2O \cdot 0.2Et_2O$

C, 56.66; H, 5.84; N, 8.69

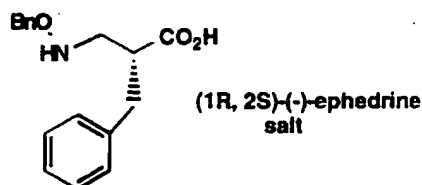
Found: C, 56.84; H, 5.22; N, 8.42.

5

Example 3

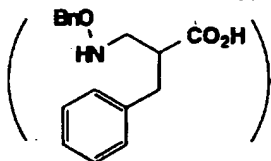


A.



10

A solution of Example 1 Part D(1) compound



(2.563 gm, 8.98 mmol) in CH_3CN (20

mL) was treated with (1R,2S)-(-)-ephedrine (1.522 gm, 9.2 mmol) and stirred until homogeneous. Most of the solvent was removed by rotary evaporation and the residue was dissolved in Et_2O (25 mL) and treated with hexane (16 mL) in portions until the mixture was slightly turbid. The solution was seeded and let stand overnight at room temperature.

15

The precipitate was collected by filtration and rinsed with 1:1 Et_2O :hexanes and dried to afford 2.101 gm of white crystals ($[a]_D = -16.4^\circ$ (c 0.6, CH_2Cl_2)). The solid (2.087 gm) was dissolved in CH_2Cl_2 , concentrated and diluted with Et_2O (18 mL) and hexane (8 mL) and seeded. The precipitate was collected by filtration and washed with 1:1- Et_2O :hexanes followed by hexanes to give title

20

25

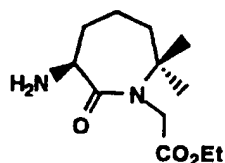
compound (1.995 gm) which was diastereomerically enriched in one isomer but not diastereomerically pure ($[\alpha]_D = -17.0^\circ$ (c 0.6, CH_2Cl_2)).

5 mp 110-114°C

Material suitable for x-ray crystallographic analysis was obtained by repeated recrystallization of the solid from CH_3CN . mp 117-119°C;

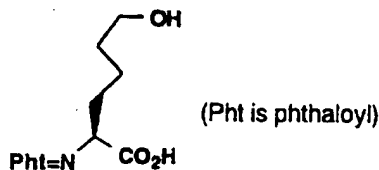
10 ($[\alpha]_D = -19.7^\circ$ (c 0.4, CH_2Cl_2)).

B.



15

B(1).



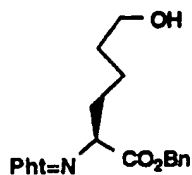
To a stirred solution of L-(+)-hydroxynor-leucine (75 g, 509.6 mmole) and sodium carbonate (54 g, 509.6 mmole) in water (900 ml) at room temperature under argon was treated with N-ethoxycarbonyl-phthalimide (111.7 g, 509.6 mmole). After being stirred for 2.0 hours, the resulting solution was filtered through a pad of celite. The filtrate was cooled in an ice bath and carefully acidified to pH=3 with 6N HCl solution. The white solid which had precipitated was filtered and dried over P_2O_5 in vacuo to afford Compound 1 (124.5 g) in 88.1% yield.

30

M.P. 162°C

^1H -NMR (DMSO): $\delta = 1.32$ (m, 6H), 2.13 (m, 2H), 4.38 (s, OH), 5.75 (m, 1H), 7.92 (m, 4H) ppm

B(2).

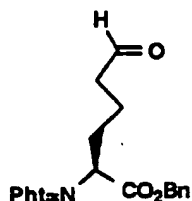


5 To a stirred slurry of Part B(1) compound (124.5 g, 0.449 mole) and cesium carbonate (73.2 g, 0.225 mole) in DMF (1.25 L) at room temperature under argon was added benzyl bromide (98.4 g, 0.575 mole). After 2.5 hours, the resulting solution was
 10 poured into EtOAc (3.0 L), washed with water (3X), 5% LiCl solution and brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo to afford title compound (142 g) as an oil in 86.1% yield.

15 1H -NMR ($CDCl_3$): δ = 1.50 (m, 4H), 2.32 (m, 2H), 3.62 (m, 2H), 4.91 (dd, 1H), 5.22 (d, 2H), 7.31 (m, 5H), 7.77 (m, 2H), 7.86 (m, 2H) ppm

^{13}C -NMR ($CDCl_3$): 22.62, 28.46, 31.91, 52.32, 62.32, 67.46, 123.55, 128.06, 128.31, 128.53, 131.77, 134.23, 135.28, 167.76, 169.25 ppm
 20

B(3).



25

To a stirred and chilled ($-78^\circ C$, Dry ice-IPA bath) oxalyl chloride solution (2.0 M solution in CH_2Cl_2 , 16.3 ml, 32.6 mmole) under argon was added dropwise a solution of dimethyl sulfoxide
 30 (4.64 ml, 65.32 mmole) in dry CH_2Cl_2 (10 ml). After the addition was complete, the solution was

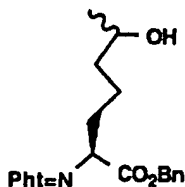
stirred at -78° for 15 minutes, then treated with a solution of Part B(2) compound (10g, 27.22 mmole) in dry CH_2Cl_2 (70 ml), stirred at -78° for another 15 minutes and slowly treated with triethylamine (16 ml). The resulting solution was stirred at -78° for 15 minutes, gradually warmed up to 0° , poured into 1:1 EtOAc-Et₂O (500 ml), washed with 1.0 N HCl solution, water and brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo to afford title compound (10 g) as a light yellow oil in 100% yield.

$^1\text{H-NMR}$ (CDCl_3): δ = 1.66 (m, 2H), 2.40 (m, 4H), 4.90 (dd, 1H), 5.18 (d, 2H), 7.35 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H), 9.72 (s, 1H) ppm

$^{13}\text{C-NMR}$ (CDCl_3): 18.66, 27.99, 42.87, 51.83, 67.47, 123.50, 128.00, 128.26, 128.44, 131.58, 134.21, 135.04, 167.55, 168.80, 201.31 ppm

20

B(4).



A stirred and chilled (0°C , ice bath) solution of Part B(3) compound (10.1 g, 27.64 mmole) in dry CH_2Cl_2 (100 ml) under argon was treated with a solution of trimethylaluminum (2.0 M solution in hexane, 23.4 ml, 46.8 mmole). The resulting solution was stirred for 45 minutes, quenched with 100 ml of a saturated NH_4Cl solution (foaming) and partitioned between 1:1 Et₂O-water (400 ml). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (2x150 ml). The organic extracts were combined, washed

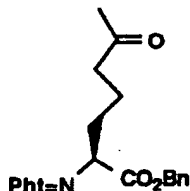
with brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo to afford title compound (10.3 g) as a gum in 98.7% yield.

5 TLC: Silica gel, 6:4 EtOAc-hexane, $R_f = 0.42$, UV and PMA.

^1H -NMR (CDCl_3): $\delta = 1.12$ (d, 3H), 1.43 (m, 4H), 3.73 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30
10 (m, 5H), 7.76 (m, 2H), 7.86 (m, 2H) ppm

^{13}C -NMR (CDCl_3): 22.5, 23.40, 28.47, 28.59, 38.20, 38.34, 52.20, 67.35, 67.51, 123.43, 127.94, 128.19, 128.41, 131.65, 134.11, 135.16, 167.62, 167.67,
15 169.13 ppm

B(5).



20 To a stirred and chilled (-78°C , Dry ice-IPA bath) oxalyl chloride solution (2.0 M solution in CH_2Cl_2 , 257.3 ml, 514.6 mmole) under argon was added CH_2Cl_2 (300ml). To this solution, a solution of dimethyl sulfoxide (80.4 g, 1.03 mole) in dry
25 CH_2Cl_2 (30 ml) was added dropwise. After the addition was complete, the reaction mixture was stirred at -78° for 20 minutes, treated with a solution of Part B(4) compound (151 g, 395.88 mmole) in dry CH_2Cl_2 (700 ml), stirred at -78°C for
30 another 20 minutes and slowly treated with triethylamine (300 ml). The resulting solution was stirred at -78° for 15 minutes, gradually warmed up to 0° , poured into 1:1 EtOAc-Et₂O (3 L), washed with 1.0 N HCl solution, water and brine, dried
35 over anhydrous Mg_2SO_4 and evaporated in vacuo to

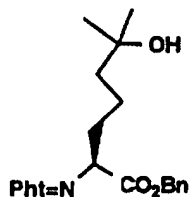
afford title compound (149.4 g) as a yellow oil in 99.5% yield.

5 TLC: Silica gel, 6:4 EtOAc-hexane, R_f =0.5, UV and PMA.

^1H -NMR (CDCl_3): δ = 1.60 (m, 2H), 2.10 (s, 3H), 2.26 (m, 2H), 2.47 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.84 (m, 2H) 10 ppm

^{13}C -NMR (CDCl_3): 20.15, 27.93, 29.84, 42.47, 51.89, 67.40, 123.46, 127.97, 128.23, 128.43, 131.61, 134.17, 135.10, 167.57, 168.93, 207.80 ppm 15

B(6).



A chilled (-78°C, Dry ice-IPA Bath) and stirred solution of titanium(IV) chloride (112.05 g, 590.65 mmole) in CH_2Cl_2 (1.5 L) under argon was treated with methylmagnesium chloride (3 M solution in THF, 196.9 ml, 590.65 mmole). The black solution was allowed to warm up to -35°C and a solution of Part B(5) compound (149.4g, 393.77 mmole) was added dropwise. After the addition was complete, the resulting solution was allowed to warm up to 0°C, stirred at 0°C for 2 hours and quenched with saturated NH_4Cl solution. The CH_2Cl_2 layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2x700 ml). The CH_2Cl_2 extracts were combined, washed with brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo. The black residue was passed through a pad of silica

gel (E. Merck, 230-400 mesh, 900 g) eluting with EtOAc-hexane (1:1) to afford a tlc-homogeneous title compound (144.8 g) as a yellow oil in 93% in yield.

5

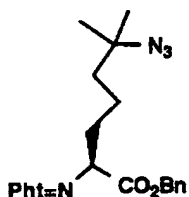
TLC: Silica gel, 1:1 EtOAc-hexane, R_f =0.4, UV and PMA.

^1H -NMR (CDCl_3): δ =1.14 (s, 6H), 1.45 (m, 4H), 2.30 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H) ppm

^{13}C -NMR (CDCl_3): 20.88, 29.00, 29.17, 42.78, 52.13, 67.35, 70.47, 123.44, 127.95, 128.19, 128.41, 131.66, 134.11, 167.66, 169.14 ppm

15

B(7).



20 A stirred solution of Part B(6) compound (44.3 g, 364.89 mmole) and azidotrimethylsilane (63.06 g, 547.34 mmole) in dry CH_2Cl_2 (2.2 L) at room temperature under argon was treated with boron trifluoride diethyl etherate (67.32 g, 474.36 mmole). After being stirred for 5 days, the resulting solution was quenched with water (1.5 L). The organic layer was separated, washed with saturated NaHCO_3 solution, water and brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo. The residue was chromatographed on a column of silica gel (E. Merck, 230-400 mesh, 700 g) eluting with EtOAc-hexane (1:3) to afford a tlc-homogeneous title compound (124.9 g) as a light yellow oil in 81.3% yield.

25

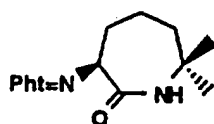
30

TLC: Silica gel, 3:7 EtOAc-hexane, R_f =0.5, UV and PMA.

5 ^1H -NMR (CDCl_3): δ =1.20 (s, 6H), 1.45 (m, 4H), 2.30 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H) ppm

^{13}C -NMR (CDCl_3): 20.97, 25.67, 25.92, 28.80,
10 40.53, 52.02, 61.16, 67.40, 123.47, 127.97, 128.23, 128.43, 131.66, 134.14, 135.12, 167.60, 169.01 ppm

B(8).



15

A solution of Part B(7) compound (124.8 g, 296.81 mmole) and 10% Pd/C (32g) in dry DMF (2.0 L) was hydrogenated for 24 hours. After completion, argon was bubbled through the reaction mixture to
20 remove excess hydrogen and methyl sulfide (2.6 ml) was added to poison the palladium. To this solution 1-hydroxybenzotriazole hydrate (46.74 g) was added and followed by ethyl-3(3-dimethylamino)-propylcarbodiimide hydrochloride salt (68.74 g).
25 The resulting solution was stirred at room temperature under argon for 3.5 hours, diluted with EtOAc (2 L) and filtered through a pad of celite. The filtrate was washed with 0.5 N HCl solution, saturated NaHCO_3 solution, and brine, dried over
30 anhydrous MgSO_4 and evaporated in vacuo to give a gum. This was triturated with Et_2O -hexane (2:1) to afford a tlc-homogeneous title compound (74.5 g) as a white solid in 87.7% yield.

35 TLC: Silica gel, 3:7 EtOAc- CH_2Cl_2 , R_f =0.35, UV and PMA.

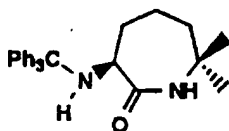
^1H -NMR (CDCl_3): δ =1.30 (s, 3H), 1.45 (s, 3H), 1.74 (m, 2H), 1.96 (m, 3H), 2.74 (m, 1H), 4.98 (d, 1H), 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H) ppm

5

^{13}C -NMR (CDCl_3): 23.89, 26.65, 29.58, 33.32, 40.68, 52.69, 54.51, 123.34, 123.15, 133.87, 168.06, 171.03 ppm

10

B(9).



A stirred solution of Part B(8) compound (74.5 g, 260.19 mmole) in a mixture of CH_3OH (900 ml) and CH_2Cl_2 (250 ml) at room temperature under argon was treated with hydrazine monohydrate (18.24 g, 364.26 mmole). After 48 hours, the solid was filtered off and the filtrate was evaporated in vacuo to give a solid (41 g).

To a stirred solution of the above solid (41 g) in CH_2Cl_2 (2 L) at room temperature under argon was added triethylamine (50 ml) and triphenylmethyl chloride (83.41 g). After 1.5 hours, the resulting slurry was diluted with EtOAc, washed with water and brine, dried over anhydrous Mg_2SO_4 and evaporated in vacuo to give a gum. This was triturated with Et₂O-pentane to give title compound (100.1 g) as a white solid in 96.5% yield.

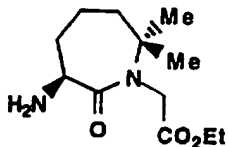
TLC: Silica gel, 6:4 EtOAc-hexane, R_f =0.53, UV and PMA.

^1H -NMR (CDCl_3): δ =1.00 (s, 3H), 1.10 (s, 3H), 1.46 (m, 6H), 3.36 (m, 1H), 4.03 (m, 1H), 5.20 (d, 1H), 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H) ppm

C^{13} -NMR ($CDCl_3$): 22.86, 25.81, 33.50, 34.23,
40.16, 51.97, 55.60, 71.89, 126.22, 127.61, 128.96,
146.48, 176.71 ppm

5

B(10).



To a stirred solution of Part B(9) compound
10 (50 g, 125 mmole) in dry THF (1020 ml) at room
temperature under argon was added simultaneously
(at same rate) a solution of lithium
bis(trimethylsilyl)amide (1.0 M solution in THF,
627.3 ml, 627.3 mmole) and a solution of ethyl
15 bromoacetate (104.8 g, 627.3 mmole) in THF (523 ml)
over the period of 1.0 hour. After the addition
was complete, the solution was stirred for 30
hours, quenched with saturated NH_4Cl solution (1.0
liter) and extracted with EtOAc (3x700 ml). The
20 EtOAc extracts were combined, washed with saturated
 $NaHCO_3$ solution and brine, dried over anhydrous
 Mg_2SO_4 and evaporated in vacuo to afford a black
oil. The experiment was repeated on the same scale
to give a similar result. The combined black oils
25 was chromatographed on a column of silica gel (E.
Merck, 230-400 mesh, 1.6 kg) eluting with EtOAc-
hexane (1:4) to give a light yellow oil. This was
dissolved in dry CH_2Cl_2 (2 L) and treated with
trifluoroacetic acid (78 ml). The solution was
30 stirred at room temperature under argon for 1.0
hour and then evaporated in vacuo at 30° . The
residue was diluted with 1.0 N HCl solution (400
ml) and washed with Et_2O (2x400 ml). The aqueous
was carefully neutralized to pH=7-8 with solid
35 $NaHCO_3$ (foaming) and extracted with CH_2Cl_2 (3x1.2

L). The CH_2Cl_2 extracts were combined, dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford a tlc homogeneous title compound (51.5 g) as a light brown oil in 84.7% yield.

5

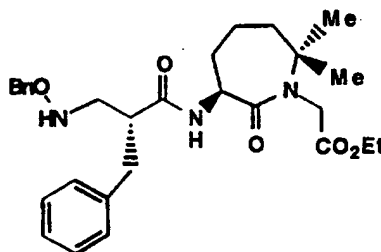
TLC: Silica gel, 8:1:1 CH_2Cl_2 - CH_3OH - AcOH , $R_f=0.3$, PMA and Ninhydrin.

^1H -NMR (CDCl_3): δ =1.28 (t, 3H), 1.36 (s, 3H), 1.38 (s, 3H) 1.60 (m, 1H), 1.90 (m, 5H), 3.75 (m, 1H), 4.00 (d, 1H), 4.22 (q, 2H), 4.28 (d, 2H) ppm

^{13}C -NMR (CDCl_3): 14.00, 20.06, 28.19, 30.07, 32.29, 39.98, 46.87, 53.20, 58.38, 60.73, 170.35, 177.06 ppm

15

C.



20

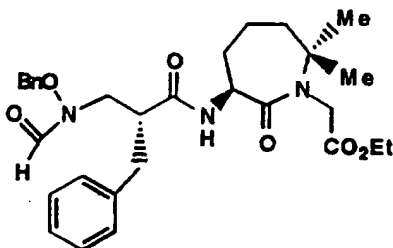
Part A compound (641 mg, 1.42 mmol) was partitioned between EtOAc and 5% KH_2PO_4 (adjusted to pH 2.5 with H_3PO_4). The layers were separated and the aqueous layer was back-extracted with EtOAc. The pooled EtOAc extracts were washed with brine, dried (Na_2SO_4), filtered and stripped to give an oil (assume 1.42 mg). The oil was dissolved in CH_2Cl_2 (10 mL) and the resulting solution was treated with Part B amine (364 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) and cooled to 0°C . The mixture was subsequently treated with HOBT hydrate (195 mg) followed by EDAC (285 mg, 1.48 mmol). After stirring at 0°C for 45 minutes and at room temperature for 45 minutes, the mixture was

25

30

partitioned between EtOAc and 5% KH_2PO_4 (adjusted to pH 2.5 with H_3PO_4). The EtOAc extract was washed successively with H_2O , 50% saturated NaHCO_3 and brine, then dried (Na_2SO_4), filtered and
5 stripped. The residue was flash chromatographed (Merck SiO_2 , 7/3-EtOAc/hexanes as eluant) to obtain title compound (427 mg, 59%, TLC R_f 0.37 (8/2-EtOAc/hexanes)) as a diastereomerically pure
10 compound. In addition, the minor diastereomer was isolated from the column (66 mg, 9%, TLC R_f 0.27 (8/2-EtOAc/hexanes)). NMR of this material was consistent with an isomer of the title compound.

D.



15

Acetic anhydride (500 μL) was added to formic acid (5.0 mL) at 0°C and the mixture was stirred for 30 minutes. Approximately 2.6 mL of
20 this solution was added to a solution of Part C compound (208 mg, 0.413 mmol) in THF (1.1 mL) at 0°C . After 30 minutes, most of the solvent was removed by rotary evaporation and the residue was partitioned between EtOAc and saturated NaHCO_3 .
25 The EtOAc extract was washed with brine, dried (Na_2SO_4), filtered and stripped to give title compound (216 mg, 97%) as an oily foam which was used directly in the next reaction without further purification.

30

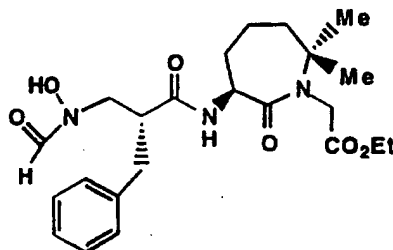
TLC R_f 0.37 (EtOAc)

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute

linear gradient (solvent A: 90% H_2O -10% MeOH -0.2% H_3PO_4 ; solvent B:0% H_2O -90% MeOH -0.2% H_3PO_4); flow rate 1.5 mL/min detecting at 220 nm; t_R = 17.2 min (100%).

5

E.

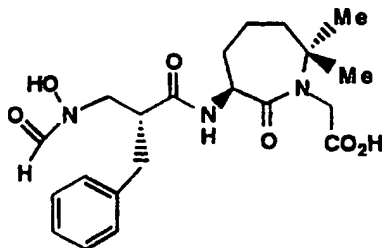


A solution of Part D compound (216 mg, 0.402 mmol) in absolute EtOH (5 mL) was hydrogenated (balloon) over 10% Pd/C (33 mg) at room temperature for 2 hours. The mixture was filtered through Celite, stripped, and azeotroped twice with EtOAc/ Et_2O /hexanes to give title compound (174 mg, 97%) as an off-white foam.

TLC R_f 0.33 (5/95-HOAc/EtOAc)
HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H_2O -10% MeOH -0.2% H_3PO_4 ; solvent B:0% H_2O -90% MeOH -0.2% H_3PO_4); flow rate 1.5 mL/min detecting at 220 nm; t_R = 12.8 min (100%).

25

F.



A stirred solution of Part E compound (168 mg, 0.376 mmol) in MeOH (3 mL) at room temperature was treated with aqueous 1 N NaOH (3 mL). An additional portion of aqueous 1 N NaOH (3 mL) was added after 3.5 hours. After a total of 6 hours, the mixture was made acidic with 5% KHSO₄ and extracted twice with EtOAc. The EtOAc extract was washed with brine, dried (Na₂SO₄), filtered and stripped. The residue was dissolved in a small amount of MeOH and EtOAc and triturated with Et₂O/hexanes to give title compound (134 mg, 86%) as an off-white solid/foam ([α]_D = +18.0° (c 0.5, CH₂Cl₂)).

TLC R_f 0.10 (5/95-HOAc/EtOAc)
HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 9.00 min (>97.4%).

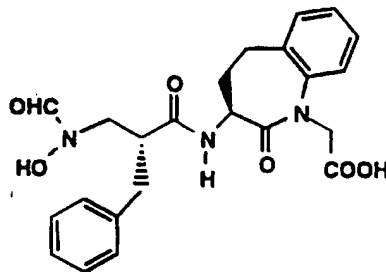
Anal. Calc'd for C₂₁H₂₉N₃O₆•0.75H₂O•0.3Et₂O

C, 58.57; H, 7.42; N, 9.23

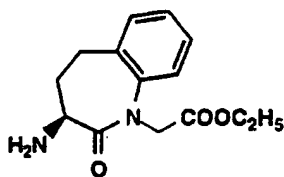
Found C, 58.31; H, 7.20; N, 8.99.

Example 4

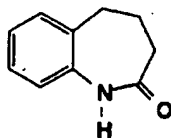
[S-(R*,R*)]-3-[[3-(Formylhydroxyamino)-1-oxo-2-(phenylmethyl)propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepine-1-acetic acid



A.



A(1).



5

Solid sodium azide (26.0 g., 0.2 mole) was introduced into a 3-neck round-bottom flask with an overhead stirrer, made into a paste with warm water (26 ml), layered with chloroform (160 ml) and cooled down to 0° (ice-salt bath). The mixture was treated dropwise with concentrated sulfuric acid (11.2 ml, 0.5 eq.) over a period of 10 minutes, stirred for an additional 10 minutes then decanted into a flask containing anhydrous sodium sulfate. The dried solution was filtered through a glass wool plug in a funnel into a 500-ml round-bottom flask. Titration of an aliquot (1.0 ml) with 1.0 N NaOH using phenolphthalein as an indicator gave a normality of 1.7 N for the hydrazoic acid.

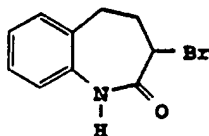
Tetralone (15.94 g, 0.108 mole) was added to the hydrazoic acid solution (0.136 mole or 1.25 eq.), heated to 40-45° (oil bath) then treated dropwise with 36.0 N H₂SO₄ (28.7 ml, 5 eq.) over a period of 1.0 hour. (Intense bubbling took place with each drop added for the first 30 minutes). The reaction mixture was cooled down to room temperature, poured into H₂O (720 ml) and stirred for 5 minutes. The solution was then extracted with EtOAc (3 x 250 ml) and the combined organic extracts were washed with brine (100 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried in vacuo. The crude product (17.819 g)

was recrystallized from CH₂Cl₂ (70 ml) and Hexane (400 ml) to give title compound as off-white precipitates (10.017 g; m. pt. 138-140°C) with consistent ¹H-NMR and ¹³C-NMR spectral data.

5 The mother liquor was chromatographed on a silica gel column (Merck, 240 g), eluting the column with EtOAc:Hexane (1:4) to give an additional amount of 5.058 g (total yield= 15.075 g, 85.6 %).

10 TLC: R_f 0.37 (Silica gel; EtOAc:Hexane-1:1; UV).

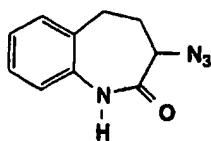
A(2).



15 A solution of Part A(1) compound (1.0 g, 6.20 mmoles) in dry CHCl₃ (15 ml) was cooled down to 0°C (ice-salt bath), treated with PCl₅ (1.5 g, 7.20 mmoles) followed by I₂ (15 mg) then stirred at 0°C under argon for 30 minutes. The yellow
20 solution was treated with Br₂ (0.39 ml or 1.2 g, 7.51 mmoles), warmed up to room temperature and refluxed under argon for 4.0 hours. The mixture was then poured into ice-water (20 g), stirred and the phases were separated, washing the aqueous
25 phase with CHCl₃ (25 ml). The combined organic extracts were washed with H₂O (5.0 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck, 70
30 g), eluting the column with EtOAc:Hexane (1:9) to give title compound as off-white precipitates (1.137 g., m.pt. 170-172°, 70.1 %) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.13 (Silica gel; EtOAc:Hexane -1:4; UV).

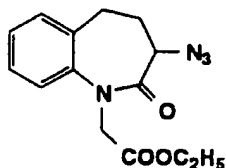
35

A(3).



A solution of Part A(2) compound (936 mg, 3.9 mmoles) and NaN₃ (300 mg, 4.6 mmoles) in dry dimethylsulfoxide (20 ml) was stirred at 60° (oil bath) under argon for 6.0 hours. The reaction mixture was cooled down to room temperature, poured into cold water (125 ml), stirred for 15 minutes and filtered, washing the solids formed with water. The crude product was dried in vacuo at 60° over drierite for 24 hours to give title compound (725 mg, m.pt. 150-152°, 91.9 %) as an off-white solid with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.58 (Silica gel; EtOAc:Hexane- 1:4 then 1:1; UV).

A(4).

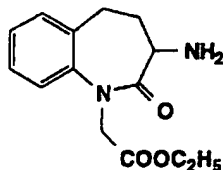


20

A solution of Part A(3) compound (10.858 g, 53.7 mmoles) in dry tetrahydrofuran (100 ml) was treated with Bu₄NBr (1.791 g, 5.56 mmoles) and powdered KOH (3.937 g, 70.2 mmoles) followed by ethyl bromoacetate (6.8 ml, 61.3 mmoles). The reaction mixture was stirred at room temperature under argon for 1.5 hours then partitioned between H₂O (196 ml) and CH₂Cl₂ (2 x 375 ml). The combined organic extracts were washed with H₂O (2 x 196 ml) and brine (100 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product was combined with the crude product mixture from a previous run (2.936 g, 12.86

mmole scale) and chromatographed on a silica gel column (Merck), eluting the column with Toluene:EtOAc (98:2) and EtOAc:Hexane (1:9) to give title compound as a solid (15.48 g, 93.5%)¹ with
5 consistent ¹H-NMR and ¹³C-NMR spectral data.
TLC: R_f 0.63 (Silica gel; EtOAc:Hexane- 1:2; UV).

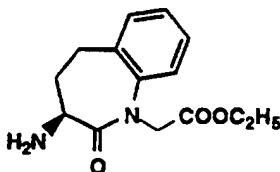
A(5).



10

A solution of Part A(4) compound (8.95 g, 31.0 mmoles) in absolute ethanol (50 ml) was treated with 10% Pd/C (443 mg) and hydrogenated at 45 psi for 3.5 hours, venting the Parr bottle every
15 30 minutes for the first 1.5 hours. The mixture was filtered through a Celite® pad in a millipore unit, washing the pad well with absolute ethanol (3 x 50 ml). The clear filtrate was evaporated to dryness and dried in vacuo to give title compound
20 as a thick yellow syrup (7.929 g, 97.5%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.45 (Silica gel; CH₂Cl₂:CH₃OH- 9:1; UV).

A(6).

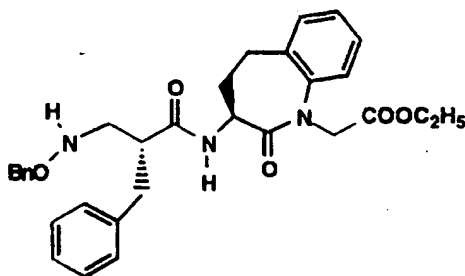


25

A solution of Part A(5) compound (14.8 g, 56.4 mmoles) and L-tartaric acid (8.50 g) in hot absolute ethanol (118 ml) was kept overnight at 0°,
30 at room temperature for 3 days and then at 0° for another 2 days. The solid that formed was recrystallized from absolute ethanol (118 ml) two

more times until a consistent specific rotation was obtained. The precipitates (6.319 g) from the second recrystallization was then suspended in EtOAc (100 ml), treated with 10% NH_4OH (12 ml) and stirred for 5 minutes. The organic phase was separated, washed with 10% NH_4OH (10 ml) and brine (15 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried *in vacuo* to give title compound as a white solid (3.927 g, m.pt. 105-107°, 26.5%) with consistent ^1H -NMR and ^{13}C -NMR spectral data.
[α]_D = -277° (c 0.99, EtOH). TLC : R_f 0.45 (Silica gel; CH_2Cl_2 : CH_3OH - 9:1; UV).

15 B.

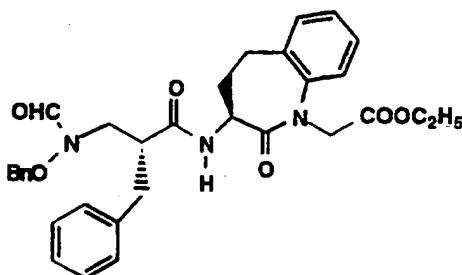


Example 3 Part A ephedrine salt (414 mg, 0.93 mmole), was partitioned between 5 % KH_2PO_4 (adjusted to pH 2.5; 4.0 ml) and EtOAc (2 x 20 ml) and the combined organic extracts were washed with brine (4.0 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried *in vacuo* to give the free acid of the Example 4 Part A compound as a clear syrup (286.6 mg, 100 % crude yield).

A solution of the above free acid (286.6 mg, 0.93 mmole) in dry CH_2Cl_2 (6.0 ml) was cooled to 0°C (ice-salt bath) and treated sequentially with a solution of the above free amine (271 mg) in dry CH_2Cl_2 , HOBT· H_2O (126.1 mg, 0.93 mmole) and EDAC (185.4 mg, 0.97 mmole). The reaction mixture was stirred at 0°C for 1.0 hour, at room

temperature for 2.0 hours, then partitioned between EtOAc (2 x 20 ml) and H₂O (4.0 ml). The organic extracts were washed with 5% KH₂PO₄ (adjusted to pH 2.5; 4.0 ml), H₂O (4.0 ml), saturated NaHCO₃ (4.0 ml) and brine (4.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried *in vacuo*. The crude product was chromatographed on a silica gel column (Merck, 70 g.), eluting the column with EtOAc:Hexane mixtures (1:3; 1:1) to give pure title compound (202 mg) and impure product. A second chromatography gave title compound as a syrup (total of 292.1 mg, 59.3%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.32 (Silica gel; EtOAc:Hexane -1:1; UV).

C.

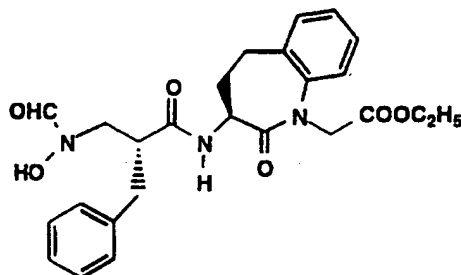


A cooled solution of HCOOH (5.0 ml) was treated with acetic anhydride (Ac₂O) (0.5 ml) and stirred at 0°C for 30 minutes. A solution of Part B compound (288 mg, 0.54 mmole) in dry THF (1.5 ml) was cooled to 0°C (ice-salt bath), treated with the above Ac₂O/HCOOH mixture (3.4 ml) and stirred at 0°C for 1.0 hour. The reaction mixture was evaporated to dryness and the residual syrup was dissolved in EtOAc (40 ml), washed with saturated NaHCO₃ (5.0 ml) and brine (5.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness, evaporated from toluene and dried *in vacuo* to give title compound as a syrup (311.3 mg, 100 %

crude) with consistent ^1H -NMR and ^{13}C -NMR spectral data. TLC: R_f 0.18 (Silica gel; EtOAc:Hexane (1:1; UV).

5

D.



A solution of Part C compound (311 mg) in CH_3OH (10 ml) was treated with 10% Pd/C (53 mg) and hydrogenated (balloon) at room temperature for 2.0 hours. The reaction mixture was diluted with CH_3OH (10 ml) and filtered through a Celite® pad in a millipore unit, washing the pad well with CH_3OH (3 x 10 ml). The clear filtrate was evaporated to dryness and dried in vacuo to give title compound as a syrup (256.7 mg, 100% crude) with consistent ^1H -NMR and ^{13}C -NMR data. TLC: R_f 0.25 (Silica gel; CH_2Cl_2 :MeOH- 9:1; UV).

20

E. [S-(R*,R*)]-3-[[3-(Formylhydroxyamino)-1-oxo-2-(phenylmethyl)propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepine-1-acetic acid

A solution of Part D compound (256.7 mg) in CH_3OH (3.5 ml) was treated with 1.0 N NaOH (2.17 ml, 4 eq) and stirred at room temperature for 1.0 hour under argon. The reaction mixture was brought to pH 1.0 with 5% KHSO_4 (9.45 ml), extracted with EtOAc (40 ml) and the organic extract washed with brine (5.0 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried in vacuo. The crude product was triturated with CH_2Cl_2 :Hexane

(1:4-25 ml) and hexane (20 ml) then dried in vacuo to give title compound as an amorphous off-white solid (215.6 mg, 90.4%) with consistent MS, IR, ^1H -NMR and analytical data. TLC: R_f 0.30 (Silica gel; EtOAc:HOAc- 95:5; UV).

$[\alpha]_D = -332.8^\circ$ (c 0.558, CH_3OH)

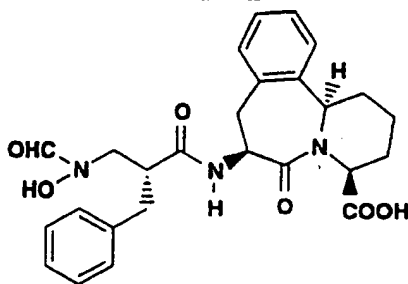
HPLC: $t_R = 5.21$ min (95.8% R isomer); $t_R = 9.58$ min (3.59% S isomer); YMC S3 ODS-A 150 x 6 mm; 220 nm, flow rate = 1.5 ml/min; 56% (10% H_2O - 90% CH_3OH - 0.2% H_3PO_4)/44% (90% H_2O - 10% CH_3OH -0.2% H_3PO_4), isocratic.

Anal. Calc'd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_6$:

C, 62.86; H, 5.73; N, 9.56

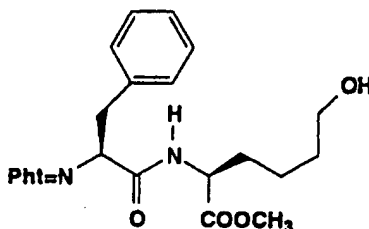
Found: C, 62.88; H, 5.98; N, 9.20.

Example 5



20

A.



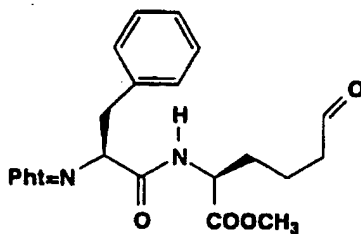
A solution of L-hydroxynorleucine (2.0 g, 13.6 mmol) in dry methanol (70 ml) was saturated with HCl gas until a clear yellow solution was obtained. The reaction mixture was cooled to room temperature, stirred for 2.0 hours, evaporated to

dryness, evaporating the syrup once from toluene (100 ml) then evaporated in vacuo to give the ester as a yellow oil. The crude ester was dissolved in dry CH_2Cl_2 (50 ml) and dry DMF (15 ml), treated with NMM (2.5 ml, 22.7 mmol) and cooled to 0°C (ice-salt bath). The mixture was treated with N-phthaloyl-L-phenylalanine (4.0 g, 13.6 mmol), HOBT $\cdot\text{H}_2\text{O}$ (1.89 g, 13.99 mmol) and EDAC (2.87 g, 14.98 mmol), stirred at 0°C for 25 minutes and at room temperature for 2.0 hours.

The reaction mixture was partitioned between EtOAc (2 x 200 ml) and H_2O (60 ml) and the combined organic extracts were washed sequentially with 0.5 N HCl (60 ml), H_2O (60 ml), 1/2 saturated NaHCO_3 (60 ml) and brine (60 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck, 200 g), eluting the column with EtOAc to give the desired product as a syrup (4.0 g). An additional 321 mg was obtained on re-chromatography of the impure fractions to give title compound (4.32 g, 73%) with consistent ^1H -NMR and ^{13}C -NMR spectral data.

TLC: R_f 0.43 (Silica gel; EtOAc; UV).

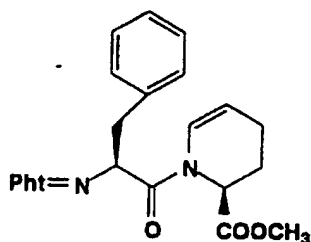
B.



A solution of oxalyl chloride (1.02 ml, 11.7 mmol) in dry CH_2Cl_2 (56 ml), was cooled to -78°C (dry-ice-acetone bath), treated with a solution of dry DMSO (1.67 ml, 21.6 mmol) in CH_2Cl_2 (2.0 ml)

- and stirred at -78°C for 20 minutes. The mixture was treated with a solution of Part A compound (4.29 g, 9.78 mmol) in dry CH_2Cl_2 (22 ml), stirred at -78°C for another 15 minutes, then
- 5 treated with triethyl-amine (8.4 ml). The reaction mixture was stirred at -78°C for 5.0 minutes, allowed to come to room temperature over a period of 45 minutes, then partitioned between EtOAc (200 ml) and 0.5 N HCl (2 x 20 ml). The organic phase
- 10 was washed with brine (40 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried *in vacuo* to give title compound as a thick syrup (4.428 g, 100% crude yield), with consistent ^1H -NMR and ^{13}C -NMR spectral data.
- 15 TLC: R_f 0.73 (Silica gel; EtOAc; UV).

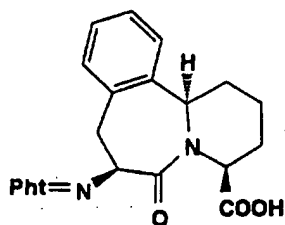
C.



- 20 A mixture of Part B compound (4.428 g, 9.78 mmol) and TFA (0.20 ml, 2.6 mmol) in dry CH_2Cl_2 (62 ml) was refluxed under argon for 2.0 hours. The reaction mixture was cooled to room
- 25 temperature, washed with 1/2 saturated NaHCO_3 (20 ml) and brine (20 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried *in vacuo*. The crude product mixture was chromatographed on a silica gel column (Merck, 200 g), eluting the column with CH_2Cl_2 :EtOAc (9:1) to give the desired
- 30 product as a syrup. The syrup was triturated with Et₂O:Hexane (2:1-60 ml) to give title compound as a white precipitate (2.92 g, 72%; m.p. $141-143^{\circ}\text{C}$) with consistent ^1H -NMR and ^{13}C -NMR spectral data.

TLC: R_f 0.67 (Silica gel; CH₂Cl₂:EtOAc-9:1; UV).

D.

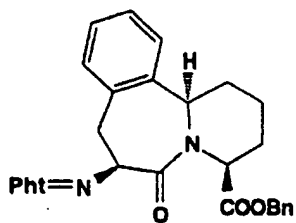


5

A solution of Part C compound (2.923 g, 6.99 mmol) in dry CH₂Cl₂ (14 ml) was treated with triflic acid (4.15 ml, 6.7 eq) and the resulting yellow solution was stirred at room temperature for 20 hours. The reaction mixture was then poured into ice-water (100 ml), extracted with EtOAc (3 x 100 ml) and the combined organic extracts washed with H₂O (2 x 25 ml) and brine (25 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product mixture was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane mixtures (1:1; 2:1) and EtOAc:HOAc (100:1). The desired fractions were combined, evaporated to dryness and dried in vacuo to give impure title compound as a solid foam (1.238 g, 42%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC : R_f 0.73 (Silica gel; EtOAc:HOAc-95:5; UV).

25

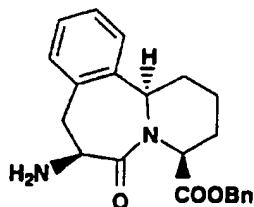
E.



A solution of Part D compound (1.238 g, 3.06 mmol) in dry DMF (3.5 ml) was treated

sequentially with benzyl bromide (0.35 ml, 2.94 mmoles) and Cs_2CO_3 (450 mg, 1.38 mmoles) then stirred at room temperature for 3.0 hours. The mixture was diluted with EtOAc (50 ml), washed with H₂O (5.0 ml), 0.5 N HCl (5.0 ml) and brine (5.0 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried in vacuo. The crude product (1.63 g) was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane (1:3) to give title compound as a syrup (586.4 mg, 39%) with consistent ^1H -NMR and ^{13}C -NMR spectral data. TLC: R_f 0.45 (Silica gel; EtOAc:Hexane-1:1; UV).

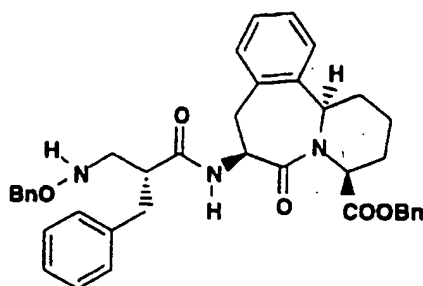
F.



15

A solution of Part E compound (586 mg, 1.18 mmoles) in dry methanol (15 ml) was treated with $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (66 μl , 1.2 eq) and stirred at room temperature for 48 hours. The reaction mixture was diluted with Et₂O (50 ml) and filtered through a millipore unit, washing the solids well with Et₂O (40 ml). The clear solution was evaporated to dryness and the solids obtained were suspended in CH_2Cl_2 (90 ml) and the solution filtered through a millipore unit, washing the solids well with CH_2Cl_2 (40 ml). The combined organic extracts were washed with brine (15 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried in vacuo to give title compound as a thick syrup (351 mg, 82 %) with a consistent ^1H -NMR spectrum. TLC: R_f 0.42 (CH_2Cl_2 :MeOH-9:1; UV, Ninhydrin)

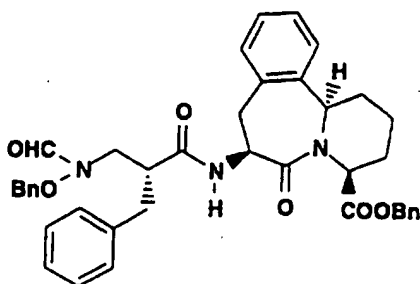
G.



Example 3 Part A ephedrine salt (538 mg,
 5 1.2 mmoles), was partitioned between 5% KH₂PO₄
 (adjusted to pH 2.5; 5.4 ml) and EtOAc (2 x 22 ml)
 and the combined organic extracts were washed with
 brine (5.4 ml), dried (anhydrous Na₂SO₄), filtered,
 evaporated to dryness and dried in vacuo to give
 10 the free acid of the ephedrine salt as a clear
 syrup (323 mg, 100% crude yield).

A solution of the free acid in dry
 CH₂Cl₂ (8.0 ml) was cooled to 0°C (ice-salt bath)
 and treated sequentially with a solution of Part F
 15 compound (351 mg, 0.96 mmole) in dry CH₂Cl₂ (2.0
 ml), HOBT·H₂O (163 mg, 1.2 mmoles) and EDAC (240
 mg, 1.25 mmoles). The reaction mixture was stirred
 at 0°C for 1.0 hour, at room temperature for 1.5
 hours, then partitioned between EtOAc (40 ml) and
 20 H₂O (5.0 ml). The organic extracts were washed
 with 5 % KH₂PO₄ (adjusted to pH 2.5; 5.0 ml), H₂O
 (5.0 ml), saturated NaHCO₃ (5.0 ml) and brine (5.0
 ml), dried (anhydrous Na₂SO₄), filtered, evaporated
 to dryness and dried in vacuo. The crude product
 25 (810 mg) was chromatographed on a silica gel
 column (Merck), eluting the column with
 EtOAc:Hexane (1:3) to give pure title compound
 (494 mg, 65%) as a solid foam with consistent ¹H-
 NMR and ¹³C-NMR spectral data.
 30 TLC: R_f 0.45 (Silica gel; EtOAc:Hexane -1:1; UV).

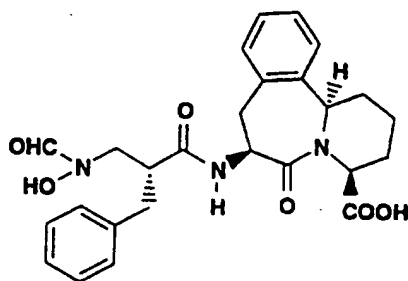
H.



A cooled solution (0°C, ice-salt bath) of
 5 HCOOH (5.0 ml) was treated with Ac₂O (0.5 ml) and
 stirred at 0°C for 30 minutes. A solution of Part
 G compound (493 mg, 0.78 mmole) in dry THF (2.2 ml)
 was cooled to 0°C (ice-salt bath), treated with the
 above Ac₂O/HCOOH mixture (4.9 ml) and stirred at
 10 0°C for 1.5 hours. The reaction mixture was
 evaporated to dryness, evaporated from Et₂O (50 ml)
 and the residual syrup was dissolved in EtOAc (60
 ml), washed with saturated NaHCO₃ (7.0 ml) and
 brine (7.0 ml), dried (anhydrous Na₂SO₄), filtered,
 15 evaporated to dryness, evaporated from toluene and
 dried in vacuo to give title compound as a syrup
 (558.3 mg, 100 % crude) with consistent ¹H-NMR and
¹³C-NMR spectral data.
 TLC: R_f 0.2 (Silica gel; EtOAc:Hexane-1:1; UV).

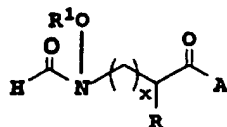
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I.



A solution of Part H compound (535 mg, 0.78
 25 mmole) in CH₃OH (15 ml) was treated with 10 % Pd/C
 (83 mg) and hydrogenated (balloon) at room

- temperatur for 4.0 hours. The reaction mixture was diluted with CH₃OH (15 ml) and filtered through a celite pad in a millipore unit, washing the pad well with CH₃OH (3 x 15 ml). The clear filtrate
- 5 was evaporated to dryness and dried in vacuo to give a syrup (354.8 mg) which was triturated with CH₂Cl₂:Hexane (1:5-30 ml) and hexane (25 ml) then dried in vacuo. Title compound was obtained as an off-white solid foam (348.5 mg, 90%).
- 10 TLC: R_f 0.38 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV).
MS (M+H)⁺ = 480
[α]_D = +44.6° (c 0.52, CH₃OH)
- 15 HPLC : t_R = 11.72 min (95.9%); YMC S3 ODS-A 150 x 6 mm; 220 nm, flow rate = 1.5 ml/min; 55% (10% H₂O- 90% CH₃OH- 0.2% H₃PO₄)/ 45% (90% H₂O- 10% CH₃OH- 0.2% H₃PO₄), isocratic.
- 20 Anal. Calc'd for C₂₆H₂₉N₃O₆•0.4 H₂O•0.14 Hexane (Eff. Mol. Wt. = 497.08):
C, 64.63; H, 6.83; N, 8.46
Found: C, 64.24; H, 6.43; N, 8.12
- 25 The following are examples of additional compounds of the invention which may be prepared employing procedures set out hereinbefore and in the working Examples.



Example
No.

R¹

x

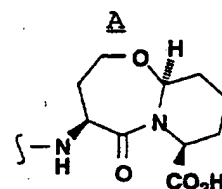
R

6

H

1

CH₂Ph

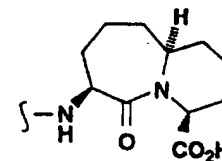


7

H

1

CH₂Ph



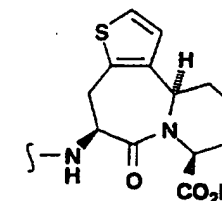
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8

H

1

CH₂CH(CH₃)₂

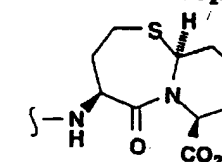


9

H

1

CH₂Ph

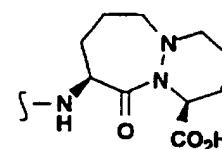


10

H

1

CH₂CH(CH₃)₂

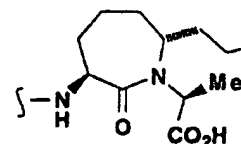


11

H

1

CH₂Ph

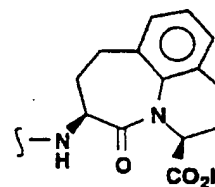


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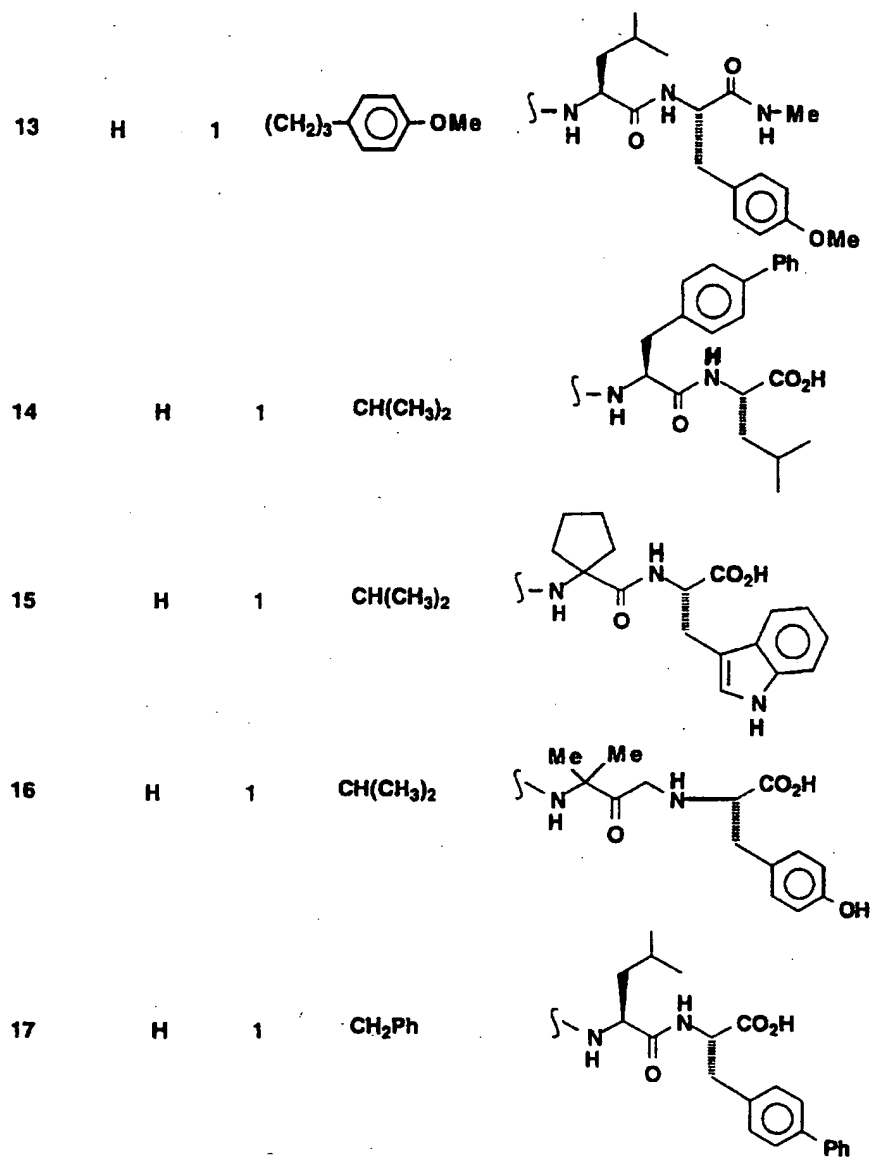
H

1

CH₂Ph



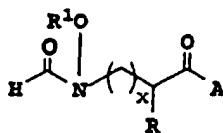
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5

What is claimed is:

1. A compound of the formula



- 5 including a pharmaceutically acceptable salt thereof wherein

x is 0 or 1,

R is H, alkyl, alkenyl, aryl-(CH₂)_p-, heteroaryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, or

- 10 R can be joined together with the carbon to which it is attached to form a 3 to 7 membered ring which may optionally be fused to a benzene ring;

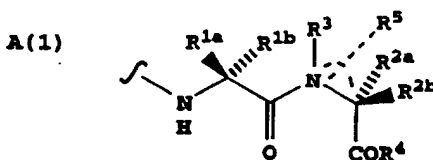
R¹ is H or -COR² where R² is alkyl, aryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, heteroaryl-

- 15 (CH₂)_p-, alkoxy or cycloalkyl-(CH₂)_p-;

p is 0 or an integer from 1 to 8; and

A is a dipeptide derived from one or two non-proteinogenic amino acids or is a conformationally restricted dipeptide mimic.

- 20 2. The compound as defined in Claim 1 wherein A is a dipeptide derivative of the structure



- 25 wherein R^{1a}, R^{1b}, R^{2a} and R^{2b} are independently selected from H, alkyl, aryl-(CH₂)_p-, cycloalkyl, cycloheteroalkyl-(CH₂)_p-, heteroaryl-(CH₂)_p-, biphenylmethyl, or

- 30 R^{1a} and R^{1b} or R^{2a} and R^{2b} may be joined together to the carbon to which it is attached to form a 3 to 7 membered ring, optionally fused to a



benzene ring; and $-\text{N}-$ refers to an optional 5 or 6 membered ring containing a single hetero atom and which may optionally include an R^5 substituent which is H, alkyl, aryl- $(\text{CH}_2)_p$,

5 cycloalkyl- $(\text{CH}_2)_p$, cycloheteroalkyl- $(\text{CH}_2)_p$ or cycloheteroaryl- $(\text{CH}_2)_p$;

R^3 is H, alkyl or aryl- $(\text{CH}_2)_p$;

R^4 is OH, Oalkyl, Oaryl- $(\text{CH}_2)_p$ or $\text{NR}_1(\text{R}_2)$

where R_1 and R_2 are independently H, alkyl, aryl,
10 aryl $(\text{CH}_2)_p$ or heteroaryl $(\text{CH}_2)_p$;

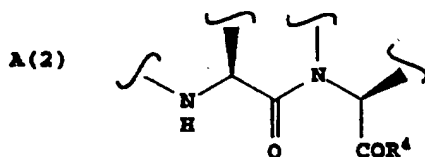
with the proviso that in A(1) at least one of



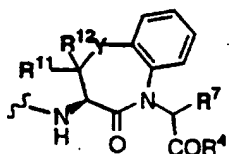
15 is other than a natural α -amino acid.

3. The compound as defined in Claim 1 wherein A is a conformationally restricted dipeptide mimic.

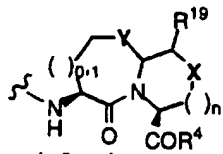
4. The compound as defined in Claim 3
20 wherein the conformationally restricted dipeptide mimic has the structure



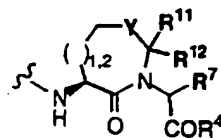
25 5. The compound as defined in Claim 3 wherein A has the formula



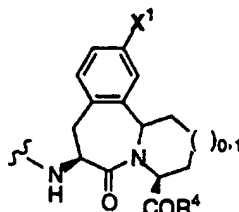
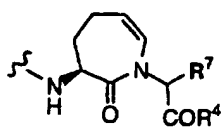
where Y = O, S, CH₂
or S(O)_{0,1,2}



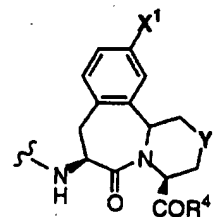
n is 0 or 1
where X = CH₂ and
Y = O, S, CH₂ or S(O)_{0,1,2}
and X = O, S when n = 1



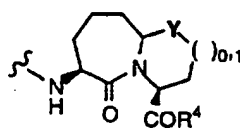
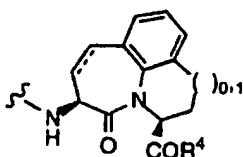
where Y = O, S, CH₂
or S(O)_{0,1,2}



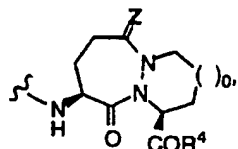
where X¹ = H, Ph,
NHSO₂R⁵
(R⁵ H)



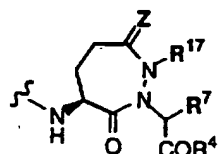
where Y¹ = O, S, NH
or S(O)_{0,1,2}
where X¹ = H, Ph,
NHSO₂R⁵
(R⁵ H)



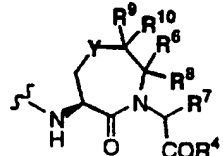
where Y = O, S, CH₂
or S(O)_{0,1,2}



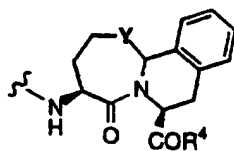
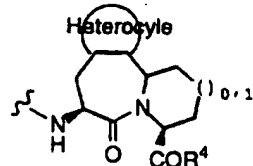
where Z = O or H, H



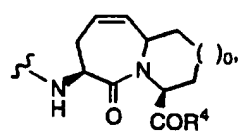
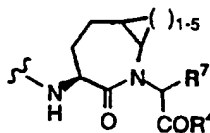
where Z = O or H, H

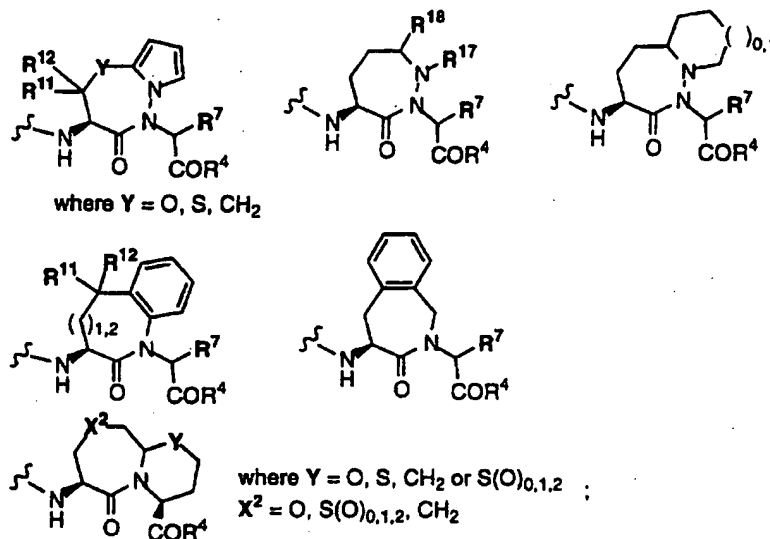


where Y = O, S, CH₂
or S(O)_{0,1,2}



where Y = O, S, NH
or S(O)_{0,1,2}



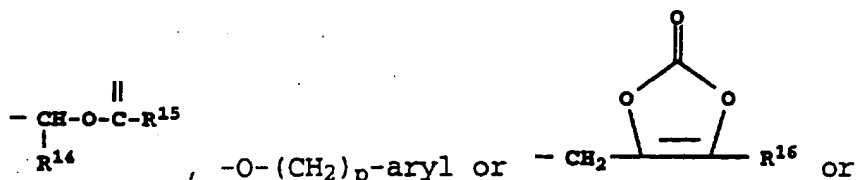


- with respect to A(5), R¹¹ and R¹² are
- 5 independently selected from hydrogen, alkyl, alkenyl, cycloalkyl -(CH₂)_p-, aryl -(CH₂)_p-, and heteroaryl -(CH₂)_p-, or R¹¹ and R¹² taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, or
- 10 R¹¹ and R¹² taken together with the carbon to which they are attached complete a keto substituent,

- with respect to A(13), R⁸, R⁹ and R⁷ are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl -(CH₂)_m-, aryl-(CH₂)_m-, and
- 15 heteroaryl-(CH₂)_m-;

- R¹⁰ and R⁶ are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl -(CH₂)_p-, aryl-(CH₂)_p-, and heteroaryl-(CH₂)_p-, or R⁶ and R¹⁰ taken together with the carbons to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, R⁶ and R⁸ taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons, or R⁹ and R¹⁰ taken together with the carbon to which they are attached complete a saturated cycloalkyl
- 20 ring of 3 to 7 carbons;
- 25 they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons;

R⁴ is OH, Oalkyl, O-(CH₂)_p-heteroaryl,



NR₁(R₂) where R₁ and R₂ are independently H, alkyl, aryl, aryl-(CH₂)_p or heteroaryl;

R¹⁴ is hydrogen, alkyl, cycloalkyl, or

5 phenyl;

R¹⁵ is hydrogen, alkyl, alkoxy or phenyl;

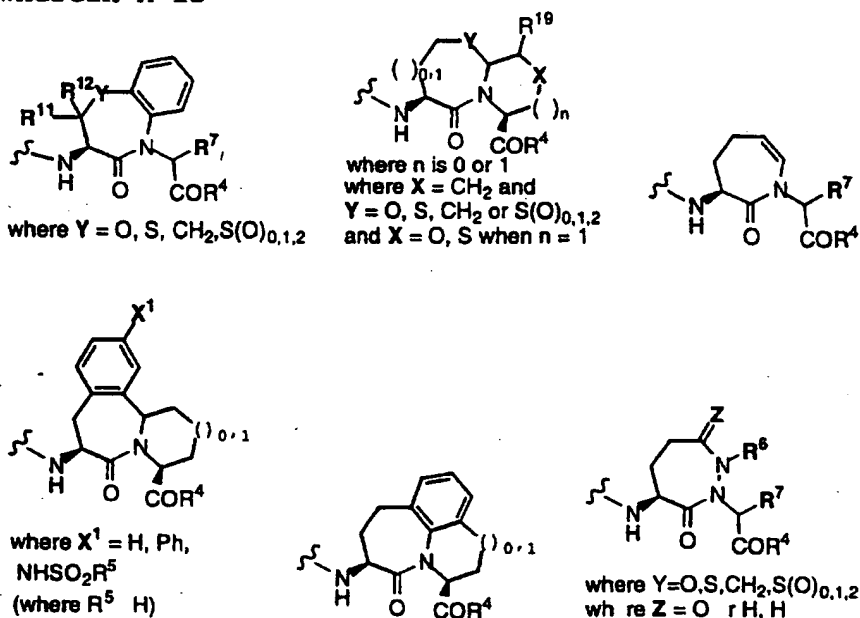
R¹⁶ is alkyl or aryl-(CH₂)_m-; and

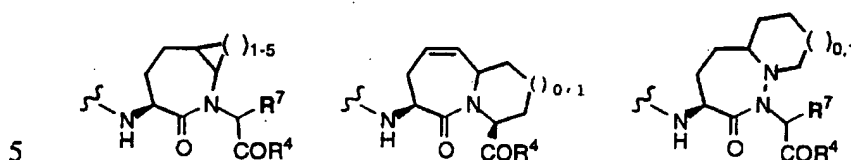
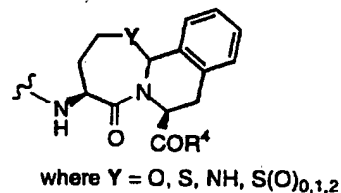
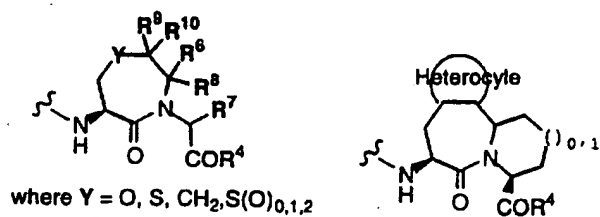
R¹⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl-(CH₂)_m-, aryl-(CH₂)_m-, or
10 heteroaryl-(CH₂)_m-.

R¹⁸ is H or alkyl or alkenyl, and R¹⁸ and R¹⁷ may be taken together with the carbon and nitrogen to which they are attached to complete a saturated N-containing ring of 5 or 6 ring members.

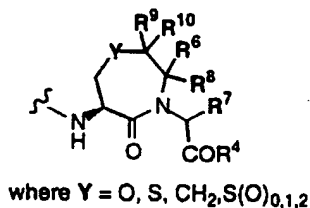
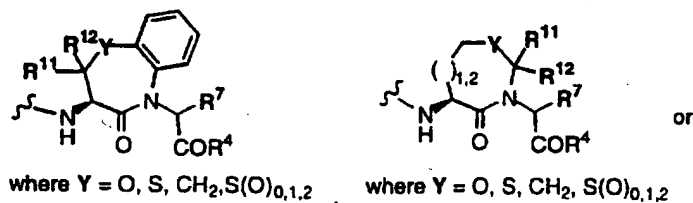
15 R¹⁹ is H or an alkyl, and in A(4), R¹⁹ and X (which is CH₂) together with the carbons to which they are attached may form an aromatic ring of carbons (as in A(15)).

6. The compound as defined in Claim 1
20 wherein A is



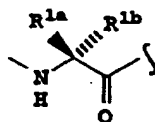


7. The compound as defined in Claim 6 wherein A is



8. The compound as defined in Claim 1 wherein R¹ is H, R is alkyl or arylalkyl, R⁴ is OH.

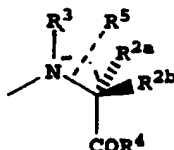
9. The compound as defined in Claim 2
where in A(1)



is a non-proteinogenic amino acid portion.

10. The compound as defined in Claim 9 wherein R^{1a} and R^{1b} are independently alkyl or arylalkyl, or R^{1a} and R^{1b} together with the carbon to which they are attached form a 3 to 7 membered ring; or one of R^{1a} and R^{1b} is biphenylmethylene and the other is biphenylmethylene or H.

11. The compound as defined in Claim 9 where in A(1),



10 is a non-proteinogenic amino acid where R^3 is H, alkyl or arylalkyl,

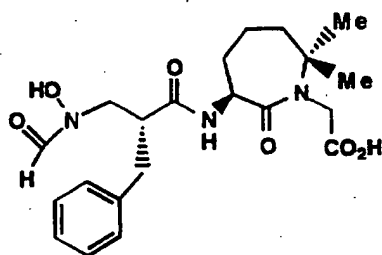
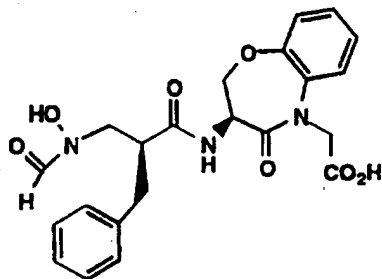
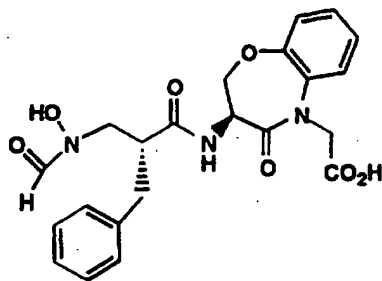
R^{2a} and R^{2b} are independently selected from H, alkyl, aryl or arylalkyl, with at least one of R^{2a} and R^{2b} being other than H, or R^{2a} and R^{2b} together with the carbon to which they are attached form a 3 to 7 membered ring.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

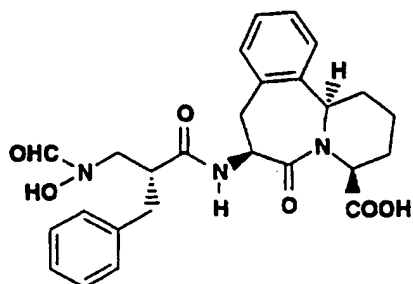
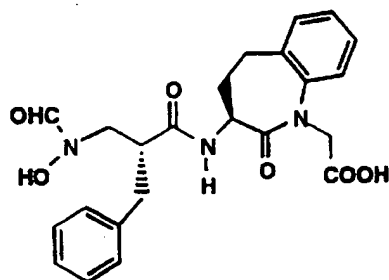
13. The pharmaceutical composition as defined in Claim 12 useful in the treatment of cardiovascular diseases such as hypertension and/or congestive heart failure.

14. A method of treating a cardiovascular disease such as hypertension and/or congestive heart failure, which comprises administering to a mammalian species a therapeutically effective amount of a composition as defined in Claim 12.

15. The compound as defined in Claim 1 which is



5



10 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05744

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/05
US CL :514/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,539,150 A (KATAKAMI ET AL) 03 September 1985, see entire document.	1-15
A, P	US 5,552,400 A (DOLLE ET AL) 03 September 1996, see entire document.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

01 JULY 1997

Date of mailing of the international search report

11 AUG 1997

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